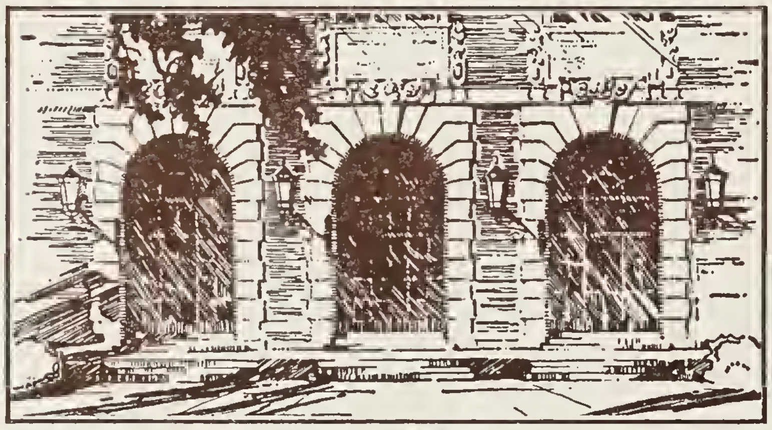

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CONTENTS.

MICHAEL SERVETUS.*

By William Osler, M. D., F. R. S.,
Regius Professor of Medicine, University of Oxford.

The year 1553 saw Europe full of tragedies, and to the earnest student of the Bible it must have seemed as if the days had come for the opening of the second seal spoken of in the Book of Revelation, when peace should be taken from the earth and men should kill one another. One of these tragedies has a mournful interest this year, the four hundredth anniversary of the birth of its chief actor; yet it was but one of thousands of similar cases with which the history of the sixteenth century is stained. On October 27, shortly after twelve o'clock, a procession started from the town-hall of Geneva—the chief magistrates of the city, the clergy in their robes, the Lieutenant Criminel and other officers on horseback, a guard of mounted archers, the citizens, with a motley crowd of followers, and in their midst, with arms bound, in shabby, dirty clothes, walked a man of middle age, whose intellectual face bore the marks of long suffering. Passing along the rue St. Antoine through the gate of the same name, the cortège took its way towards the Golgotha of the city. Once outside the walls, a superb sight broke on their view: in the distance the blue waters and enchanting shores of the Lake of Geneva, to the west and north the immense amphitheatre of the Jura, with its snow-capped mountains, and to the south and west the lovely valley of the Rhone; but we may well think that few eyes were turned away from the central figure of that sad procession. By his side, in earnest entreaty, walked the aged pastor, Farel, who had devoted a long and useful life to the service of his fellow citizens. Mounting the hill, the field of Champel was reached, and here on a slight eminence was the fateful stake, with the dangling chains and heaping bundles of faggots. At this sight the poor victim prostrated himself on the ground in prayer. In reply to the exhortation of the clergyman for a specific confession of faith, there was the cry, 'Misericordia, misericordia! Jesu, thou Son of the eternal God, have compassion upon me!' Bound to the stake by the iron chain, with a chaplet of straw and green twigs covered with sulphur on his head, with his long dark face, it is said that he looked like the Christ in whose name he was bound. Around his waist were tied a large bundle of manuscript and a thick octavo printed book. The torch was applied, and as the flames spread to the straw and sulphur and flashed in his eyes, there was a piercing cry that struck terror into the hearts of the bystanders. The faggots were green, the burning was slow, and it was long before in a last agony he cried again, 'Jesu, thou Son of the eternal God, have mercy upon me!' Thus died, in his forty-fourth year, Michael Servetus Villanovanus, physician, physiologist, and heretic. Strange, is it not, that could he have cried, 'Jesu, thou Eternal Son of God!' even at this last moment, the chains would have been unwound, the chaplet removed, and the faggots scattered; but he remained faithful unto death to what he believed was the *Truth* as revealed in the Bible.

* This address did double duty—at the Johns Hopkins Hospital Historical Club, and as an Extension lecture in the Summer School, Oxford.

The story of his life is the subject of my address.

Michael Servetus, known also as Michel Villeneuve, or Michael Servetus Villanovanus, or, as he puts in one of his books, *alias* Reves, was a Spaniard born at Villanueva de Sigena, in the present province of Huesca. When on trial at Vienna, he gave Tudela, Navarre, as his birthplace, at Geneva, Villanueva of Aragon; and at one place he gave as the date of his birth 1509, and at the other 1511. The former is usually thought to be the more correct. As at Villanueva de Sigena there are records of his family, and as the family altar, made by the father of Servetus, still exists, we may take it that at any rate the place of his birth is settled. The altar-screen is a fine piece of work, with ten paintings. I am indebted to Signor Antonio Virgili, of Barcelona, for the photograph of it here reproduced (Fig. 2). Servetus seems to have belonged to a good family in easy circumstances, and at his trial he said he came of an ancient race, living nobly.

From the convent school he probably went to the neighbouring University of Saragossa. Possibly he may have studied for the priesthood, but however that may be be, there is evidence that he was a precocious youth, and well read in Latin, Greek, and Hebrew, the last two very unusual accomplishments at that period.

We next hear of him at Toulouse, studying canon and civil law. He could not have been twenty when he entered the service of the Friar Quintana, confessor to the Emperor Charles V, apparently as his private secretary. In the suite of the Emperor he went to Italy, and was present when Pope and Emperor entered Bologna, and 'he saw the most powerful prince of the age at the head of 20,000 veterans kneeling and kissing the feet of the Pope.' Here he had his first impression of the worldliness and mercenary character of the Papacy, hatred of which, very soon after, we find to have become an obsession.

In the summer of 1530 the Emperor attended the Diet of Augsburg, where the Princes succeeded in getting Protestantism recognized politically. Such a gathering must have had a profound influence on the young student, already, we may suppose, infected with the new doctrines. Possibly at Saragossa, or at Toulouse, he may have become acquainted with the writings of Luther. Such an expression of opinion as the following, written before his twenty-first year, could scarcely have been of a few months' growth: 'For my own part, I neither agree nor disagree in every particular with either Catholic or Reformer. Both of them seem to me to have something of truth and something of error in their views; and whilst each sees the other's shortcomings, neither sees his own. God in his goodness give us all to understand our errors, and incline us to put them away. It would be easy enough, indeed, to judge dispassionately of everything, were we but suffered without molestation by the churches freely to speak our minds.' (Willis.)

How far he held any personal communication with the German reformers is doubtful. It is quite possible, and Tollin, his chief biographer, makes him visit Luther. We do not know how long he held service with Quintana, Tollin thinks a year and a half. It is not unlikely that the good friar was glad to get rid of a young secretary infected with heresy so shocking as that contained in his first book, published in 1531; indeed, there is a statement to the effect that a monk in the suite of Quintana found the book in a shop at Ratisbon and hastened to tell the confessor of its terrible contents. Servetus


DE TRINITATIS ERRORIBVS LIBRI SEPTEM.

Per Michaelem Serueto, aliàs Reues ab Aragonia Hispanum.

Anno M. D. XXXI.

Fig. 3.

had plunged headlong into studies of the most dangerous character, and had even embooked them in a small octavo volume, entitled *De Trinitatis Erroribus*, which appeared without the printer's name, but on the title-page the author, Michael Serveto, *alias* Reves ab Aragonia, Hispanum, and with the date MDXXXI. In the innocency of his heart he thought the work would be a good introduction to the more liberal of the Swiss reformers, but they would have none of it, and were inexpressibly shocked at its supposed blasphemies. Nor did

Fig. 1.

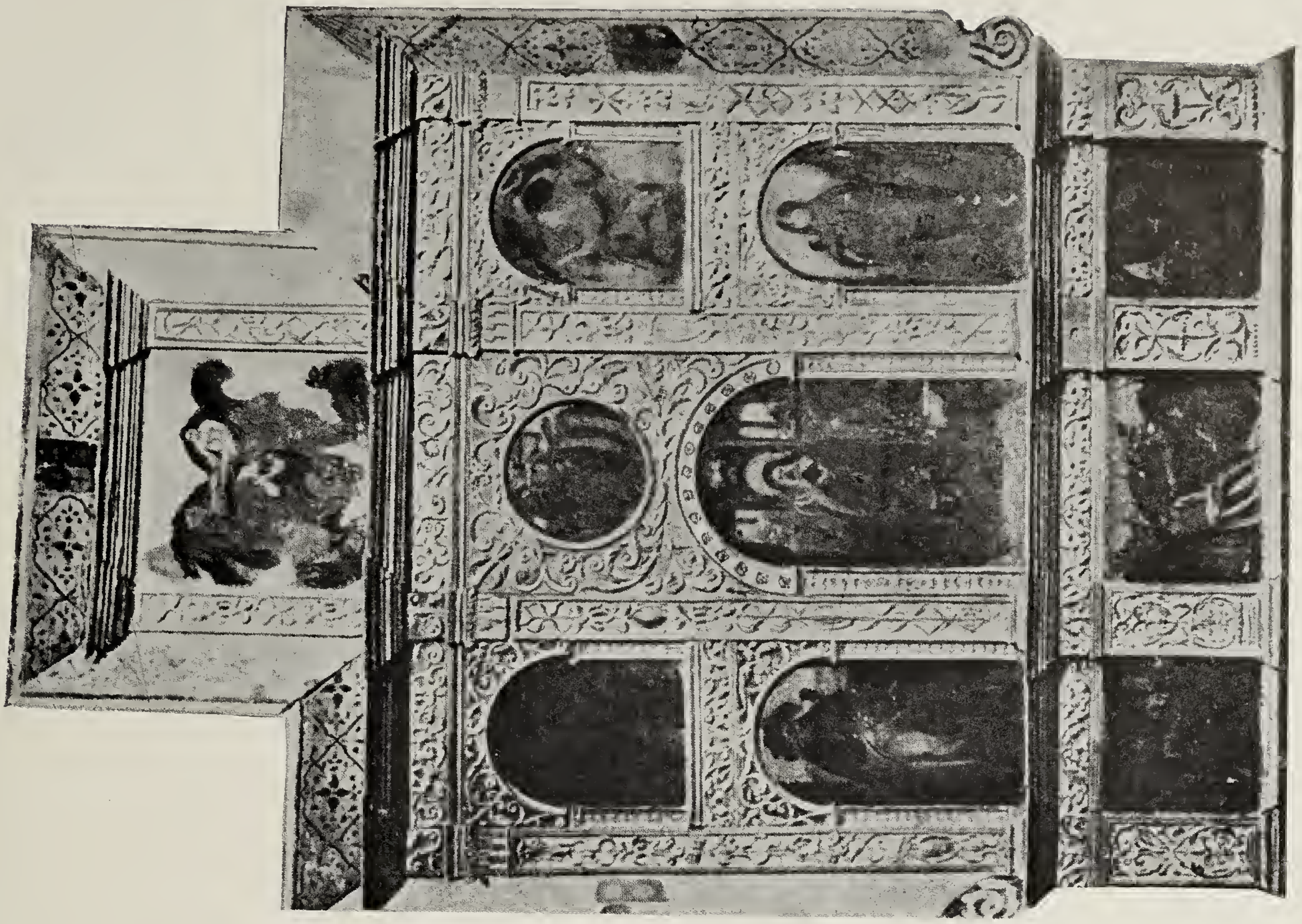


Fig. 2.—Altar Screen at Barcelona.

he fare better at Strassburg; and even the kind-hearted Bucer said that the author of such a work should be disembowelled and torn in pieces.

In thorny theological questions a layman naturally seeks shelter, and I am glad to quote the recent opinion of a distinguished student of the period, Professor Emerton,[1] on this youthful phase of the life of Servetus. 'He would not admit that the eternal Son of God was to appear as man, but only that a man was to come who should be the Son of God. This is the earliest intimation we have as to the speculations which were occupying the mind of the young scholar. It is highly significant that from the start he was impressed with what we should now call the historical view of theology. As he read the Old Testament, its writers seemed to him to be referring to things that their hearers would understand. Their gaze into the future was limited by the fortunes of the people at the moment. To imagine them possessed of all the divine mysteries, and to have in mind the person of the man Jesus as the ultimate object of all their prophetic vision, was to reflect back the knowledge of history into a past to which such knowledge was impossible. So far as I can understand him, this is the key to all of Servetus' later thought. His manner of expressing himself is confusing and intricate to the last degree, so much so that neither in his own time nor since has any one dared to say that he understood it. To his contemporaries he was a half-mad fanatic; to those who have studied him, even sympathetically, his thought remains to a great extent enigmatical; but this one point is fairly clear: that he grasped, as no one up to his time had grasped, this one central notion, that, whatever the divine plan may have been, it must be revealed by the long, slow movement of history—that, to understand the record of the past, it must be read, so far as that is possible, with the mind of those to whom it was immediately addressed, and must not be twisted into the meanings that may suit the fancy of later generations.'

'To have seized upon such an idea as this—an idea which has begun to come to its rights only within our memories—was an achievement which marks this youth of twenty as at all events an extraordinary individual, a disturbing element in his world, a man who was not likely to let the authorities rest calmly in possession of all the truth there was.'

In the following year, 1532, two dialogues appeared, explanatory and conciliatory, a little book which only aggravated the offence, and feeling the Protestant atmosphere too hot, Servetus went to Paris. Dropping this name by which he has been known, and closing this brief but stormy period, for the next twenty-one years we now follow Michel Villeneuve, or Michael Villanovanus, in a varied career as student, lecturer, practitioner, author and editor, still nursing the unconquerable hope that the world might be reformed could he but restore the primitive doctrine of the Church.

II

We know very little of this his first stay in Paris. Possibly he found employment as teacher, or as reader to the press. At this period his path first crossed that of Calvin, then a young student. Of about the same age, both ardent students, both on the high road of emancipation from the faith of their birth, they must have had many discussions on theological questions. One may conclude from the reproachful sentence of Calvin many years later, 'Vous avez fuy le luite', that arrangements had been made for a public debate.

After a short stay at Avignon and Orleans, we next find Servetus at Lyons, in the employ of the Trechsels brothers, the famous printers. Those were the days of fine editions of the classics and other books, which required the assistance of scholarly men to edit and correct. He brought out a splendid folio of Ptolemy's Geography, 1535 (Fig. 4), with commentaries on the different countries, which show a wide range of knowledge in so young a man. It is marked also by many examples of independent criticism, as, when speaking of Palestine, he says that the 'Promised Land' was anything but a 'promising land', and instead of flowing with milk and honey, and a land of corn, olives and vineyards, it was inhospitable and barren, and the stories about its fertility nothing but boasting and untruth. He seems to have been brought to task for this, as in the second edition, 1541, this section does not exist. For this work he was paid by the Trechsels 500 crowns.

It is possible that Servetus and Rabelais may have met at Lyons, as at this time the 'great Dissimulator' was physician to the Hôtel-Dieu, but there is nothing in the writings of either to indicate that their paths crossed. The man who had the greatest influence upon him at Lyons was Symphorien Champier, one of the most interesting and distinguished of the medical humanists of the early part of the sixteenth century. Servetus helped him with his French *Pharmacopocia,* and Pastor Tollin will have it that Champier even made a home for the poor scholar. An ardent Galenist, an historian, the founder of the hospital and of the medical school, Champier had the usual predilection of the student of those days for astrology. Probably from him Servetus received his instructions in the subject. At any rate, when the distinguished Professor of Medicine of Tübingen, Fuchsius, attacked Champier on the ground of his astrological vagaries, Servetus took up his pen and replied in defence with a pamphlet entitled 'In Leonhardum Fuchsium defensio apologetica pro Symphoriano Campeggio', an exceedingly rare item, the only one indeed of the writings of Servetus that I have not seen in the original.

Stimulated doubtless by the example and precept of Champier, Servetus returned to Paris to study medicine. Fairly rich in pocket with the proceeds of his literary work, he attached himself first to the College of Calvi, and afterwards to that of the Lombards, and it is said that he took the degrees of M.A. and M.D., but of this I am told that there is no documentary evidence.

Of his life in Paris we have very little direct evidence, except in connexion with a single incident. We know that he came into intimate contact with three men—Guinther of Andernach, Jacobus Sylvius, and Vesalius. Guinther and

[1] *Harvard Theological Review*, April, 1909.

Sylvius must have been men after his own heart, ripe scholars, ardent Galenists, and keen anatomists. In the *Institutiones Anatomicae* (Basel, 1539), Guinther speaks of Servetus in connexion with Vesalius, who was at this time his fellow pro-sector. 'And after him by Michael Villanovanus, distinguished by his literary acquirements of every kind, and scarcely second to any in his knowledge of Galenical doctrine.' With their help he states that he has examined the whole body, and demonstrated to the students all of the muscles, veins, arteries, and nerves. There was at this time a very keen revival in the study of anatomy in Paris, and to have been associated with such a young genius as Vesalius, already a brilliant dissector, must have been in itself a liberal education in the subject. It is easy to understand whence was derived the anatomical knowledge upon which was based the far-reaching generalization with which the name of Servetus is associated in physiology.

But the Paris incident of which we know most is connected with certain lectures on judicial astrology. We have seen that at Lyons, Servetus had defended his friend and patron Symphorien Champier, through whom he had doubtless become familiar with its practice. Though forbidden by the Church, judicial astrology was still in favour in some universities, and was practised largely by physicians occupying the most distinguished positions. In those days few were strong minded enough to defy augury, and in popular belief all were 'servile to skiey influences'. It was contrary to the regulations of the Paris Faculty to lecture on the subject, though at this time the king had in his employ a professional astrologist, Thibault. Shortly after reaching Paris Servetus began a course of lectures on the subject, which very soon brought him into conflict with the authorities.

The admirable practice for the Dean to write out each year his report, has preserved for us the full details of the procedure against Servetus. Duboulay, in his *History of the University of Paris,* vol. vi, has extracted the whole affair from the Dean's Commentary, as it is called, of the year. He says that a certain student of medicine, a Spaniard, or as he says, from Navarre, but with a Spanish father, had taught for some days in Paris in 1537 judicial astrology or divination. After having found out that this was condemned by the Doctors of the Faculty, he caused to be printed a certain apology in which he attacked the doctors, and moreover declared that wars and pests and all the affairs of men depended on the heavens and on the stars, and he imposed on the public by confounding true and judicial astrology. The Dean goes on to state that, accompanied by two of his colleagues, he tried to prevent Villanovanus from publishing the apology, and met him leaving the school where he had been making a dissection of the body with a surgeon, and in the presence of several of the scholars, and of two or three doctors, he not only refused to stop the publication, but he threatened the Dean with bitter words.

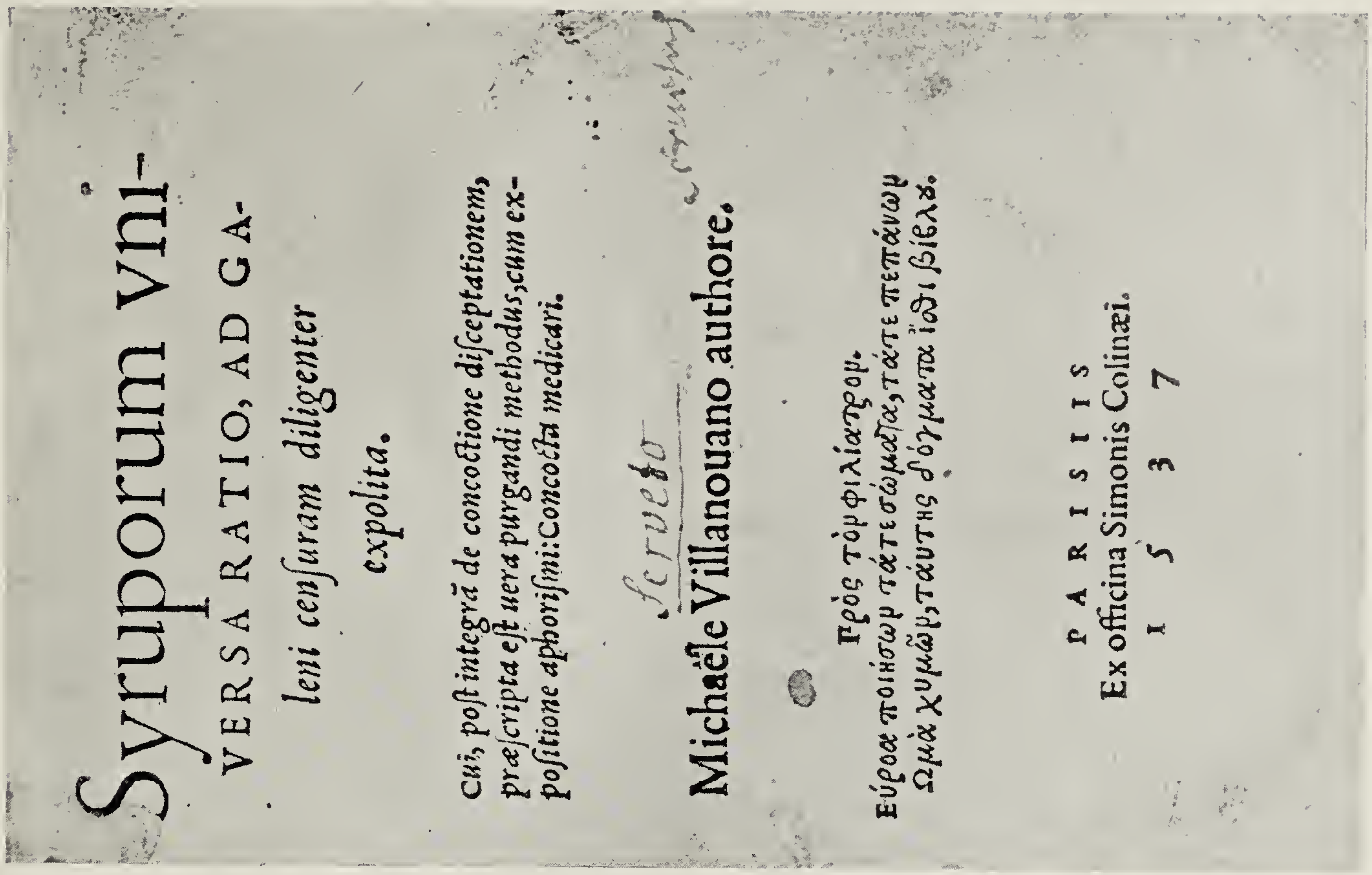
The Faculty appears to have had some difficulty in getting the authorities to move in the matter. Possibly we may see here the influence of the court astrologer, Thibault. After many attempts, and after appealing to the Theological Faculty and the Congregation of the University, the question was taken up by Parliament. The speeches of counsel for the Faculty, for the University, for Villanovanus, and for the Parliament are given in full. The Parliament decided that the printed apology should be recalled, the booksellers were forbidden to keep them, the lectures on astrology were forbidden, and Villanovanus was urged to treat the Faculty with respect. But on their part they were asked to deal with the offender gently, and in a parental fashion. It is a very interesting trial, and the Dean evidently enjoyed his triumph. He says that he took with him three theologians, two doctors in medicine, the Dean of the Faculty of Canonical Law, and the Procurator-General of the University. The affair was discussed by Parliament with closed doors.

The *Apologetica disceptatio pro astrologia,* the rarest of the Servetus items, the only copy known being in the Bibliothèque Nationale, is an eight leaf pamphlet, without title-page, pagination, or printer's name. The friends of the Faculty must have been very successful in their confiscation of the work. Tollin, who discovered the original, has reprinted it (Berlin, 1880). It was not hard for Servetus to cite powerful authorities on his side, and he summons in his defence the great quartette, Plato, Aristotle, Hippocrates, and Galen. A practical star-gazer, he took his own observations, and the pamphlet records an eclipse of Mars by the moon. He must, too, have been a student of the weather, as he speaks of giving in his lectures public predictions which caused great astonishment. The influence of the moon in determining the critical days of diseases, a favourite doctrine of Galen, is fully discussed, and he says that Galen's opinion should be written in letters of gold. He rests content with these great authorities, referring very briefly to one or two minor lights. He scoffs at the well-known bitter attack on divination by Picus.

It took several generations to eradicate completely from the profession a belief in astrology, which lingered well into the seventeenth century. In his *Vulgar Errors,* discussing the 'Canicular' or 'Dog Days', Sir Thomas Browne expresses his opinion of astrology in the most characteristic language. 'Nor do we hereby reject or condemn a sober and regulated Astrology; we hold there is more truth therein than in Astrologers; in some more than many allow, yet in none so much as some pretend. We deny not the influence of the Starres, but often suspect the due application thereof; for though we should affirm that all things were in all things; that heaven were but earth celestified, and earth but heaven terrestrified, or that each part above had an influence upon its divided affinity below; yet how to single out these relations, and duly to apply their actions, is a work oft times to be effected by some revelation, and Cabala from above, rather then any Philosophy, or speculation here below.'

Among the auditors of Servetus was a young man, Pierre Paumier, the Archbishop of Vienne, who appears to have befriended him in Paris, and who a few years later asked him to be his body physician. The astrology trial was settled in March, 1537.

Servetus cannot have been very long a student of medicine,



Syruporum vni-
VERSA RATIO, AD GA-
leni censuram diligenter
expolita.

Cui, post integrã de concoctione disceptationem, præscripta est uera purgandi methodus, cum expositione aphorismi: Concocta medicari.

Serueto

Michaële Villanouano authore.

Πρὸς τὸν φιλίατρον.
Εὔροα ποιήσων τά τε σώματα, τά τε πεπάνων
Ὠμὰ χυμῶν, ταύτης δόγματα ἴσθι βίβλου.

PARISIIS
Ex officina Simonis Colinæi.
1 5 3 7

FIG. 5.

CLAVDII PTOLEMAEI ALEXANDRINI
GEOGRAPHICAE ENARRATIONIS
LIBRI OCTO.

EX BILIBALDI PIRCKEYMHERI tralatione, sed ad Græca & prisca exemplaria à Michaële Villanouano iam primum recogniti. Adiecta insuper ab eodem Scholia, quibus exoleta urbium nomina ad nostri seculi morem exponuntur.

*

QVINQVAGINTA ILLAE QVOQVE CVM veterum tum recentium tabulæ adnectuntur, uariiq; incolentium ritus & mores explicantur.

LVGDVNI
EX OFFICINA MELCHIORIS ET
GASPARIS TRECHSEL FRATRVM.
M. D. XXXV.

FIG. 4.

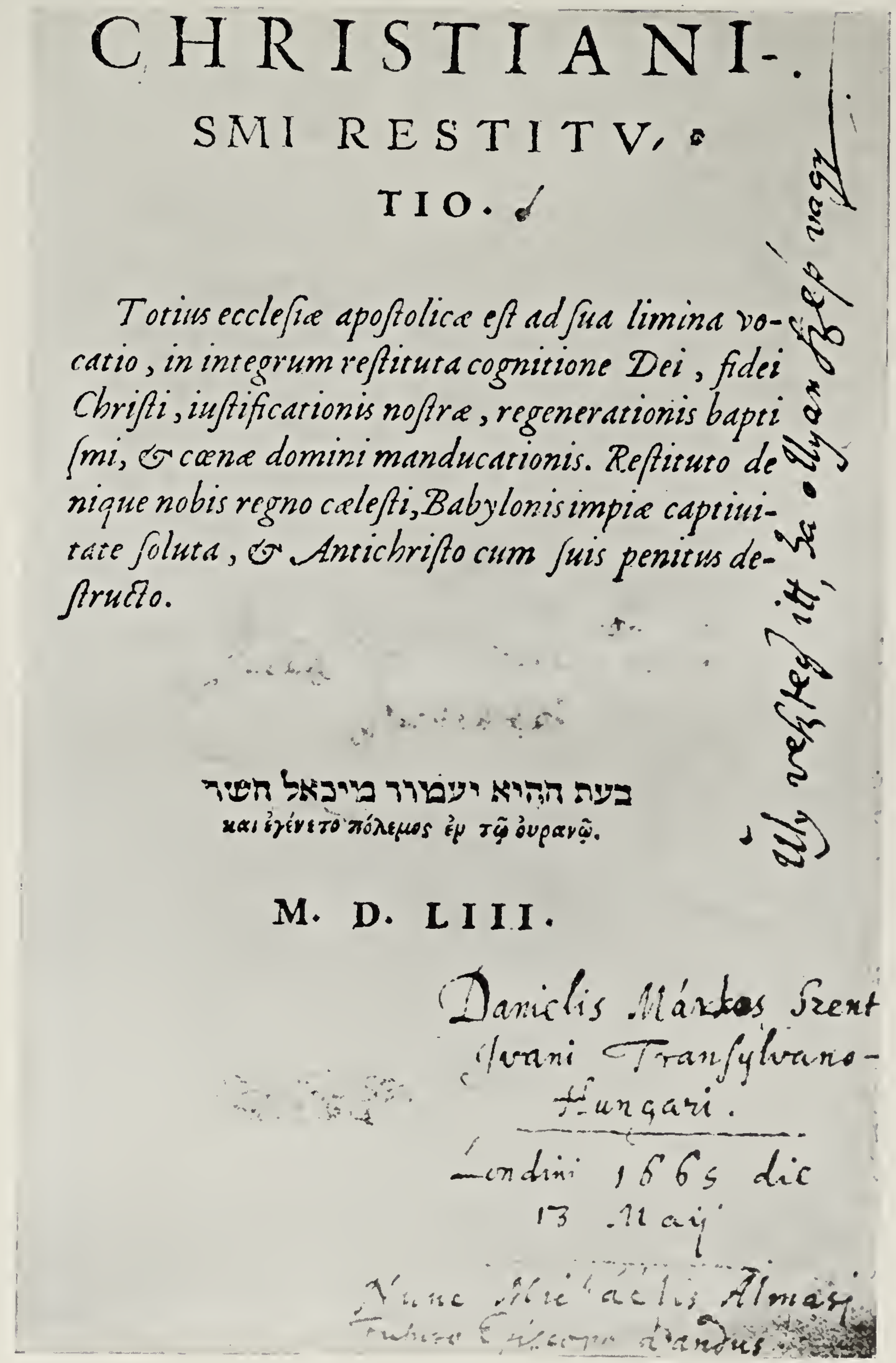
BIBLIA

ſacra ex Santis Pagnini trala-
TIONE, SED AD HEBRAI-
cæ linguæ amuſſim nouiſsimè ita recognita, &
ſcholiis illuſtrata, ut planè noua edi-
tio uideri poſsit.

Acceſsit præterea Liber interpretationum Hebraicorum, Arabicorum, Græcorumq;
nominum, quæ in ſacris literis reperiuntur, ordine alphabetico digeſtus, eodem authore.

LVGDVNI,
Apud HVGONEM à Porta.
M. D. XLII.
Cum priuilegio ad annos ſex.

Fig. 6.



CHRISTIANI-
SMI RESTITV-
TIO.

Totius eccleſiæ apoſtolicæ eſt ad ſua limina vocatio, in integrum reſtituta cognitione Dei, fidei Chriſti, iuſtificationis noſtræ, regenerationis baptiſmi, & cœnæ domini manducationis. Reſtituto deniqne nobis regno cæleſti, Babylonis impiæ captiuitate ſoluta, & Antichriſto cum ſuis penitus deſtructo.

בעת ההיא יעמוד מיכאל השר
καὶ ἐγένετο πόλεμος ἐν τῷ οὐρανῷ.

M. D. LIII.

Danielis Márkos Szent
Ivani Transylvano-
Hungari.
Londini 1665 die
13 Maij

Fig. 7.

but never lacking in assurance, he came before the world as a medical author in the little treatise on *Syrups and their use* (Fig. 5). Association with Champier, whom he had helped in an edition of his French *Pharmacopoeia*, had made him familiar with the subject. The first three chapters are taken up with the views on 'Concoctions' or 'Digestions', of which at that time a series, from the first to the fourth, was recognized. He pleads for a unity of the process, and, as Willis remarks, he makes the very shrewd remark at that day, 'that diseases are only perversions of natural functions and not new entities introduced into the body.' The greater part of the treatise is taken up with theoretical discussions on the opinions of Galen, Hippocrates, and Avicenna. The 'Composition and use of the Syrups' is deferred to the fifth and a concluding (sixth) chapter.

The little book appears to have been popular, and was reprinted twice at Venice, 1545 and 1548, and twice at Lyons, 1546 and 1547.

III

Whether the adverse decision of Parliament disgusted him with Paris, or whether through some friend the opportunity to settle in practice had offered, we next hear of Villeneuve at Charlieu, a small town about twelve miles from Lyons, where he spent a year, or part of the year 1538-9. Here his old Paris friend Paumier sought him and induced him to settle at Vienne, offering him apartments in the palace, and an appointment as his body physician. After nearly ten years of wandering, at last, in a peaceful home in the fine old Roman city, with its good society, and under the protection of the Primate of all France, Servetus spent the next fourteen years as a practising physician.

Few details of his life are known. He retained his association with the Trechsels, the printers, who had set up a branch establishment in Vienne. In 1541 he brought out a new edition of Ptolemy, with a dedication to the Archbishop. From the preface we have a glimpse of a genial group of companions, all interested in the new studies. Several critical items in the edition of 1535 disappear in the new one of 1541, e.g. the scoffing remarks about Palestine; and in mentioning the royal touch, instead of, 'I have myself seen the King touching many with this disease (i.e. Scrofula), but I have not seen that they were cured,' he says, 'I have heard that many were cured.' Perhaps he felt it unbecoming in a member of an ecclesiastical circle, and living under the patronage of the Archbishop, to say anything likely to give offence.

In the following year he issued an edition of Pagnini's Bible in a fine folio (Fig. 6). Its chief interest to us is the testimony that Servetus was still deep in theological studies, for the commentaries in the work place him among the earliest and boldest of the higher critics. The prophetic psalms, and the numerous prophecies in Isaiah and Daniel are interpreted in the light of contemporary events, but as Willis remarks, 'These numerous excessively free and highly heterodox interpretations appear to have lost Villeneuve neither countenance nor favour at Vienne.'

For another Lyons' publisher, Frelon, he edited a number of educational works, and through him the Vienne physician was put in correspondence with the Geneva reformer.

A dreamer, an enthusiast, a mystic, Servetus was possessed with the idea that could but the doctrines of the Church be reformed the world could be won to a primitive, simple Christianity. We have already seen his attempt to bring the Swiss Reformers into what he thought correct views upon the Trinity. He now began a correspondence with Calvin on this subject, and on the question of the Sacraments. The letters, which are extant, in tone and contents shocked and disgusted Calvin to such a degree that in a communication to Farel, dated February, 1546, after stating that Servetus had offered to come to Geneva, he adds, 'I will not pledge my faith to him; for did he come if I have any authority here I should never suffer him to go away alive.'

For years Servetus had in preparation the work which he fondly hoped would restore primitive Christianity. Part of a MS. of this he had sent to Calvin. Having tried in vain to get it published, he decided to print it privately at Vienne. Arrangements were made with a local printer, who set up a separate press in a small house, and in a few months 1,000 copies were printed. The title-page here reproduced (Fig. 7) has the date 1553, and on the last page the initials of his name, 'M. S. V.'

He must have known that the work was likely to cause great commotion in the Church, but he hoped that the identity of the author would be as little suspected as that the Vienne physician, Michael Villeneuve, was Michael Servetus of the heretical *de Trinitatis Erroribus*. Intended for distribution in Germany, Switzerland, and Italy, the work was made up into bales of 100 copies for distribution to the trade. Probably from their mutual friend Frelon Calvin received a couple of copies. The usual story is that through one William Trie as a medium, Calvin denounced Villeneuve to the inquisition at Vienne. This was the view of Servetus himself, and is supported by Willis, Tollin, and others; but advocates of Calvin continue to deny that there is sufficient evidence of his active participation at this stage.

There was at this time at Lyons the well-known inquisitor Orry, who ten years before had brought Étienne Dolet to the stake. No sooner had he got scent of the affair than he undertook the prosecution with his customary zeal, and Servetus was arrested. The preliminary trial at Vienne is chiefly of interest on account of the autobiographical details which Servetus gives. The evidence against him was so overwhelming that he was committed to prison. Surrounded by his friends, who must have been greatly shocked and distressed to find their favourite physician in so terrible a plight, abundantly supplied with money, with the prison discipline very lax as the jailer was his friend, it is not surprising that the day after his commitment Servetus escaped, greatly no doubt to the relief of the Archbishop and the authorities. The inquisitor had to be content with burning an effigy of the heretic with some 500 copies of his work.

From April 7 until the middle of July Servetus disappears from view, and we next meet with him, of all places in the world, at Geneva. Why he should have run this risk has been much discussed, but the explanation given by Guizot is probably the correct one. At that time the Liberals, or 'Libertines', as they were called because of their hostility to Calvin, fully expected to triumph. 'One of their leaders, Ami Perrin, was first Syndic: a man of their party, Gueroult, who had been banished from Geneva, had been corrector of the press at the time when the *Restoration of Christianity* was published, and thanks to the influence of his patrons, the Libertines, he had returned to Geneva, and would naturally be the medium between them and Servetus. Taking a comprehensive view of the whole case and the antecedents of all those concerned in it, I am convinced that Servetus, defeated at Vienne, went to Geneva, relying on the support of the Libertines, whilst they on their side expected to obtain efficacious help from him against Calvin.' He seems to have been nearly a month in Geneva before his arrest on the morning of August 14.

The full account of this famous heresy trial has lost much of its interest so far as the doctrinal details are concerned. At this distance, with our modern ideas, the procedure seems very barbarous. Servetus was cruelly treated in prison, and there is a letter from him which speaks of his shocking condition, without proper clothing, and a prey to vermin. Mademoiselle Roch has well depicted this phase of the martyr's career in her fine statue which has been erected at Anamnese, and which is here reproduced (Fig. 8). The full report of the trial may be followed in the account given by Willis, and the 'Procès-Verbal' was in existence at Geneva in manuscript.

One thing seems clear, that while at first the accusations were largely concerned with the heretical views of Servetus, later the public prosecutor laid more stress upon the political side of the case, accusing him of conspiracy with the Libertines. The trial divided Geneva into hostile camps, and it sometimes looked as though Calvin, quite as much as Servetus, was on trial. To strengthen their hands the clerical party appealed to the Swiss churches. The answer, strong enough in condemning the heresy and blasphemy, refrained from specifying the kind of punishment.

Accustomed in France to hear the Swiss Reformers branded as the worst type of heretics, Servetus appears never to have understood why he should not have been received with open arms by the Protestants, whose one desire was the same as his own, the restoration of primitive faith and practice. He made a brave fight, and brought strong countercharges against Calvin, whom he accused specifically of causing his arrest at Vienne. He offered to discuss the questions at issue publicly, an offer which Calvin would have accepted had the syndics allowed. The whole city was in a ferment, and Sunday after Sunday Calvin and the other pastors thundered from their pulpits against the blasphemies of the Spaniard. After dragging its weary length for nearly two months, the public feeling veered strongly to the side of Calvin, and on October 27 the Council, by a majority vote, resolved that in consideration of his great errors and blasphemies, the prisoner should be burnt alive.

Servetus appears to have been a curious compound of audacity and guilelessness. The announcement of the condemnation appears to have completely stunned him, as he seems never to have considered its possibility. He sent for Calvin and asked his pardon, but there was bitterness in the heart of the great reformer whose account of the interview is not very pleasant reading.

On the morning of the 27th, the Tribunal assembled before the porch of the Hôtel de Ville to read to the prisoner his formal condemnation, under ten separate heads, the two most important of which relate to the doctrine of the Trinity, and Infant Baptism. It is curious that under one of the headings he should be denounced as an arrogant innovator, and an inventor of heresies against Popery! The entreaty of Servetus for a more merciful mode of death (for which, to his credit, be it said, Calvin also pleaded) was in vain. The procession at once formed to the place of execution.

Nothing in his life, it may be said, became him like the leaving of it. As Guizot remarks, 'The dignity of the philosopher triumphed over the weakness of the man, and Servetus died heroically and calmly at that stake the very thought of which had at first filled him with terror.'

There will be dedicated next year at Vienne a monument commemorating the services of Servetus as an independent spirit in theology, and as a pioneer in physiology.

It has been said that Sappho survives because we sing her songs, and Aeschylus because we read his plays, but it would be difficult to explain the widespread interest in Servetus from any knowledge men have of his writings. The pathos of his fate, which scandalized Gibbon more profoundly than all the human hecatombs of Spain or Portugal, accounts for it in part. Then there is the limited circle of those who regard him as a martyr to the Unitarian confession; while scientific men have a very definite interest in him as one of the first to make a substantial contribution to our knowledge of the circulation of the blood. His theological and physiological views call for brief comments.

IV

Next to theology itself the study of medicine has been a great heresy breeder. From the days of Arnold of Villanova and Pierre of Abano, there have been noted heretics in our ranks. Bossuet defines a heretic as 'One who has opinions'. Servetus seems to have been charged with opinions like a Leyden jar. His most notable ones concerned the Trinity and Infant Baptism. Wracked almost to destruction in the third and fourth centuries on the subject of the Trinity, the final conquest of Arianism found its expression in that magnificent human document the Athanasian Creed, with which the Catholic Church has for ever settled the question, in language which sends a cold shudder down the backs of heretics. But there have always been turbulent souls who could not rest satisfied, and who would bring up unpleasant points from the Bible—men who were not able to accept Dante's wise advice:

—'Mad is he who hopes that our reason can traverse the infinite way which one Substance as Three Persons holds. Be content oh human race with the Quia'.

The doctrine has been a great breeding ground of heretics, the smoke of whose burning has been a sweet savour in the nostrils alike of Catholics and Protestants. Even to-day, so deeply ingrained is the catholic creed, that nearly everything in the way of doctrinal vagary is forgiven save denial of the Trinity, which is thought to put a man outside the pale of normal Christianity. If this is the feeling to-day, imagine what it must have been in the middle of the sixteenth century!

Servetus wrote two theological works—*de Trinitatis Erroribus*, published in 1531, followed by a supplement in 1532. To these I have already referred. Living a double life at Vienne, to the inhabitants he was the careful and kind practitioner of medicine, to whom they had become devoted, but all the while, nourishing the dream of his youth, he had in preparation a work which he believed would win the world to Christ by purifying the Church from grave errors in doctrine.

I have already spoken of the printing of the *Christianismi Restitutio.* Mainly concerned with most abstruse questions concerning the Trinity and Infant Baptism, it is a most difficult work to read, and, as theologians confess, a still more difficult one to understand. Professor Emerton, in his article from which I have already quoted, gives in a few paragraphs the essence of his views. 'He finds the central fact of Christion speculation, not in the doctrine of the Trinity as formulated by the schools, but in the fact of the divine incarnation in the person of Jesus. He admits the divine birth, explaining it as in harmony with a general law of divine manifestation whereby the spiritual is revealed in the material. He would not accept the idea of an eternal sonship, except in this sense, that the divine Word, the Logos, had always been active as the expression in outward form of the divine activity. So, in the fullness of time, this same Logos produced a being from a human mother upon whom at the moment of his birth the divine Spirit was breathed. Obviously this is not the "eternal Son" of the creeds, and herein lay the special theological crime of Servetus. In his criticism of the church order, of the papal government, of the sacramental system, he does not differ essentially from the more radical of the reformers. On the essential matters of baptism and the Eucharist he goes quite beyond the established reforming churches. In both cases he invokes the principle of plain reason. He rejects Infant Baptism on the ground that the infant can have no faith, and that the practice is therefore mere incantation. He denies transubstantiation on the rational basis that substances and accidents may not be separated, and does not spare the reforming leaders for what seemed to him their half-hearted attitude on this point. His language throughout is harsh and violent, except where, as at the close of his chapters, he passes over into the forms of devotion and closes his diatribes with prayers of great beauty and spirituality.'

The Christian Church early found out that there was only one safe way of dealing with heresy. From the end of the fourth century, when the habit began, to its climax on St. Bartholomew's Day, it was universally recognized that only dead heretics ceased to be troublesome. History affords ample evidence of the efficacy of repressive measures, often carried out on a scale of noble proportions. France is Catholic because of a root and branch policy; England's Protestantism is an enduring testimony to the thoroughness with which Henry VIII carried out his measures. As De Foe says in his famous pamphlet, *Shortest way with Dissenters*, if a man is obstinate and persists in having an opinion of his own, contrary to that held by a majority of his fellows, and if the opinion is pernicious and jeopardizes his eternal salvation, it is much safer to burn him than to allow his doctrines to spread! For 1,200 years this policy kept heresy within narrow limits until the great outbreak. The very best men of the day were consenting to the death of heretics. The spirit of Protestantism was against it; Luther nobly so. Judged by his age Servetus was a rank heretic, and as deserving of death as any ever tied to a stake. We can scarcely call him a martyr of the Church.—What Church would own him? All the same, we honour his memory as a martyr to the truth as he saw it.

Servetus was a student of medicine in Paris with Sylvius and Guinther, two of the most ardent of the revivers of the Galenic anatomy. More important still, he was a fellow student and pro-sector with Vesalius. He wrote one little medical book of no special merit. The works which he edited, which brought him more money than fame, indicate an independent and critical spirit. Vienne was a small town, in which we cannot think there was any scientific stimulus, though it was in a region noted for its intellectual activity.

In possession of a fact in physiology of the very first moment, Servetus described it with extraordinary clearness and accuracy. But so little did he think of the discovery, of so trifling importance did it appear in comparison with the great task in hand of restoring Christianity, that he used it simply as an illustration when discussing the nature of the Holy Spirit in his work *Christianismi Restitutio.* The discovery was nothing less than that of the passage of the blood from the right side of the heart to the left through the lungs, what is known as pulmonary, or lesser circulation.

In the year 1553 the views of Galen everywhere prevailed. The great master had indeed effected a revolution in the knowledge of the circulation almost as great as that made by Harvey in the seventeenth century. Briefly stated there were two bloods, the natural and the vital, in two practically closed systems, the veins and the arteries. The liver was the central organ of the venous system, the 'shop' as Burton calls it, in which the chylus was converted into blood and from which it was distributed by the veins to all parts of the body for nourishment. The veins were rather vessels containing the blood than tubes for its transmission—irrigating canals Galen called them. Galen knew the structure of the heart, the arrangement of its valves, and the direction in which the blood passed, but its chief function was not, as we suppose, mechanical, but in the left ventricle, the seat of life, the vital spirits

were generated, being a mixture of inspired air and blood. By an alternate movement of dilatation and collapse of the arteries the blood with the vital spirits were kept in constant motion.[2] Galen had demonstrated that the arteries and the veins communicated with each other at the periphery. A small quantity of the blood went, he believed, from the right side of the heart to the lungs, for their nourishment, and in this way passed to the left side of the heart; but the chief communication between the two systems was through pores in the ventricular septum, the thick muscular wall separating the two chief chambers of the heart.

The literature may be searched in vain for any other than the Galenic view up to 1553. Even Vesalius, who could not understand from its structure how even the smallest quantity of blood could pass through the septum dividing the ventricles, offered no other explanation. The more one knows of the Galenic physiology, the less one is surprised that it had so captivated the minds of men. The description of the new way which Servetus describes is found in the fifth book of the *Christianismi Restitutio,* in which he is discussing the nature of the Holy Spirit. After mentioning the threefold spirit of the body of man, natural, vital, and animal, he goes on to discuss the vital spirit, and in a few paragraphs describes the pulmonary circulation. 'Rightly to understand the question here, the first thing to be considered is the substantial generation of the vital spirit—a compound of the inspired air with the most subtle portion of the blood. The vital spirit has, therefore, its source in the left ventricle of the heart, the lungs aiding most essentially in its production. It is a fine attenuated spirit, elaborated by the power of heat, of a crimson colour and fiery potency—the lucid vapour as it were of the blood, substantially composed of water, air, and fire; for it is engendered, as said, by the mingling of the inspired air with the more subtle portion of the blood which the right ventricle of the heart communicates to the left. This communication, however, does not take place through the septum, partition, or midwall of the heart, as commonly believed, but by another admirable contrivance, the blood being transmitted from the pulmonary artery to the pulmonary vein, by a lengthened passage through the lungs, in the course of which it is elaborated and becomes of a crimson colour. Mingled with the inspired air in this passage, and freed from fuliginous vapours by the act of expiration, the mixture being now complete in every respect, and the blood become fit dwelling-place of the vital spirit, it is finally attracted by the diastole, and reaches the left ventricle of the heart.

'Now that the communication and elaboration take place in the lungs in the manner described, we are assured by the conjunctions and communications of the pulmonary artery with the pulmonary vein. The great size of the pulmonary artery seems of itself to declare how the matter stands; for this vessel would neither have been of such a size as it is, nor would such a force of the purest blood have been sent through it to the lungs for their nutrition only; neither would the heart have supplied the lungs in such fashion, seeing as we do that the lungs in the foetus are nourished from another source—those membranes or valves of the heart not coming into play until the hour of birth, as Galen teaches. The blood must consequently be poured in such large measures at the moment of birth from the heart to the lungs for another purpose than the nourishment of those organs. Moreover, it is not simply air, but air mingled with blood that is returned from the lungs to the heart by the pulmonary veins.

'It is in the lungs, consequently, that the mixture (of the inspired air with the blood) takes place, and it is in the lungs also, not in the heart, that the crimson colour of the blood is acquired. There is not indeed capacity of room enough in the left ventricle of the heart for so great and important an elaboration, neither does it seem competent to produce the crimson colour. To conclude, the septum or middle portion of the heart, seeing that it is without vessels and special properties, is not fitted to permit and accomplish the communication and elaboration in question, although it may be that some transudation takes place through it. It is by a mechanism similar to that by which the transfusion from the *vena portae* to the *vena cava* takes place in the liver, in respect of the blood, that the transfusion from the pulmonary artery to the pulmonary vein takes place in the lungs, in respect of the spirit' (Willis's translation). I here reproduce from the Vienna example the two pages from which the greater part of this description is taken (Figs. 9 and 10).

The important elements here are: First, the clear statement of the function of the pulmonary artery; secondly, the transmission of the impure or venous blood through the lungs from the right side of the heart to the left; thirdly, the recognition of an elaboration or transformation in the lungs, so that with the freeing the blood of 'fuliginous vapours', there was at the same time a change to the crimson colour of the arterial blood; fourthly, the direct denial of a communication of the two bloods, by means of orifices in the septum between the ventricles.

He had no idea of the general or systematic circulation, and so far as the left heart and the arteries were concerned he believed them to be the seat of the vital blood and spirits.

It is not hard to imagine how Servetus had become emancipated from the old views. A student at Paris at a most opportune period, when dissection had become popular, he had had as pro-sector to Guinther exceptional opportunities. But more important still, he had as fellow worker the anatomical archheretic, Andreas Vesalius, already imbued with the conviction that his teachers were wrong in regarding Galen as inspired and infallible. It was at this very period that Vesalius had

[2] So firmly entrenched was the Galenic physiology that the new views of Harvey made at first very slow progress. In Burton's *Anatomy of Melancholy,* which is a sort of epitome of medical knowledge of the seventeenth century, is the following description: 'The left creek (i. e. ventricle) has the form of a cone, and is the seat of life, which, as a torch doth oil, draws blood unto it begetting of it spirits and fire, and as a fire in a torch so are spirits in the blood; and by that great artery called aorta, it sends vital spirits over the body, and takes air from the lungs.'

Fig. 8—Servetus in Prison.

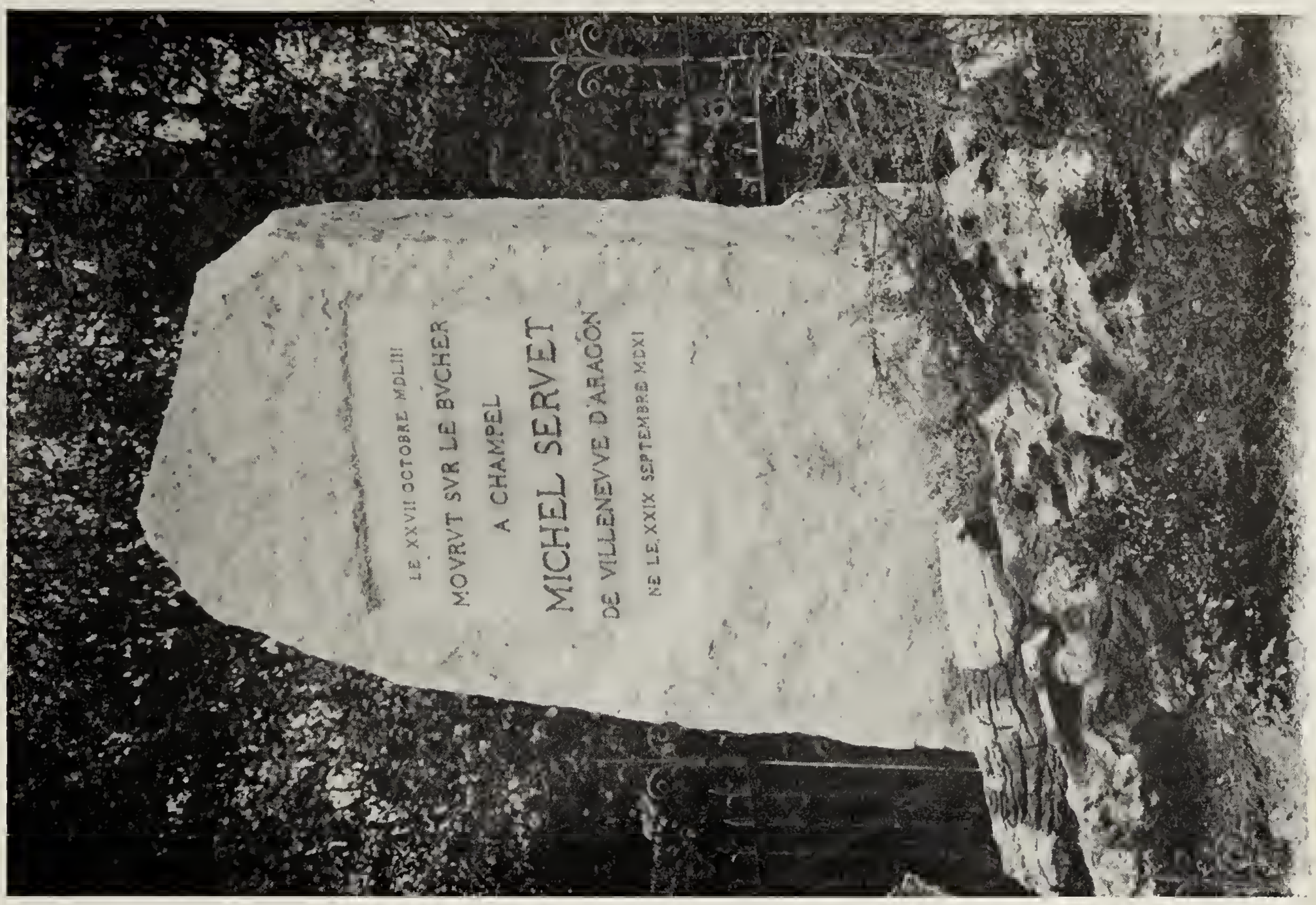


Fig. 11.

pointed out to his teacher Sylvius the error of Galen about the aortic valves; and when one considers the extraordinary rapidity with which Vesalius reformed human anatomy, before he had completed his twenty-eighth year, it is not surprising that his colleague and co-worker should have discovered one of the great truths of physiology.

The *Christianismi Restitutio* was never published, and the discovery of Servetus remained unrecognized until the attention of Wotton was called to it by Charles Bernard, a St.

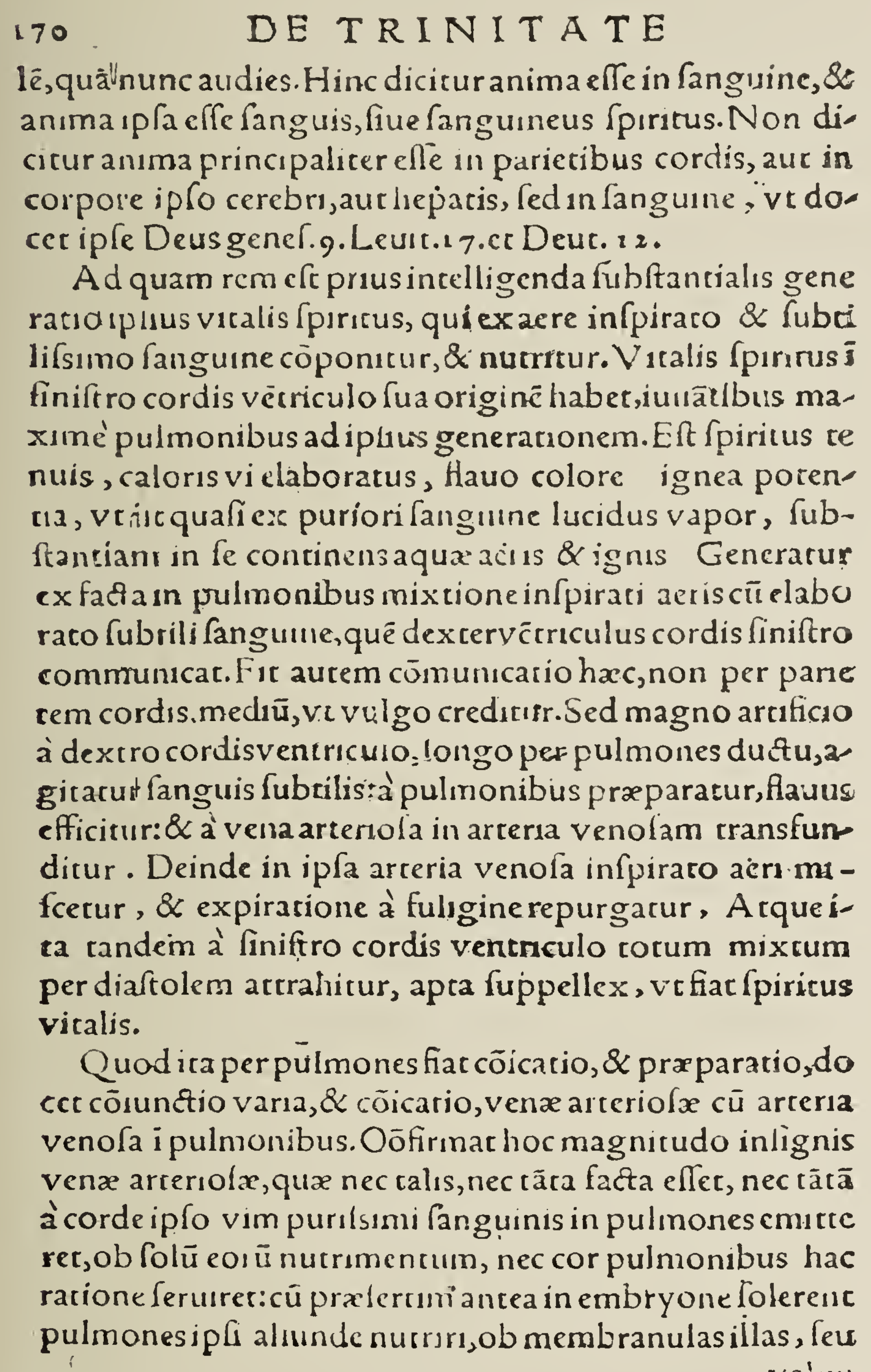


FIG. 9.

Bartholomew's Hospital surgeon.[3] Meanwhile it had been rediscovered, and among the many vagaries with which the history of the circulation of the blood is marked, not the least striking is the attempt to rob Servetus of his credit. In 1559 there was published a work by Realdus Colombo,[4] a student of Vesalius and his successor at Padua, in which the circulation of the blood from the right side of the heart to the left is clearly described. It is impossible to say that he had added anything to the account just given, and the far-fetched view has been maintained that Italian students at Paris had acquainted Servetus with the views of Colombo. It is claimed for Colombo also that he had a better idea of the function of respiration in the purification of the blood, by its mingling with the air, but Servetus distinctly states that the mixture takes place in the lungs, not, as was usually understood at the time, in the heart itself.

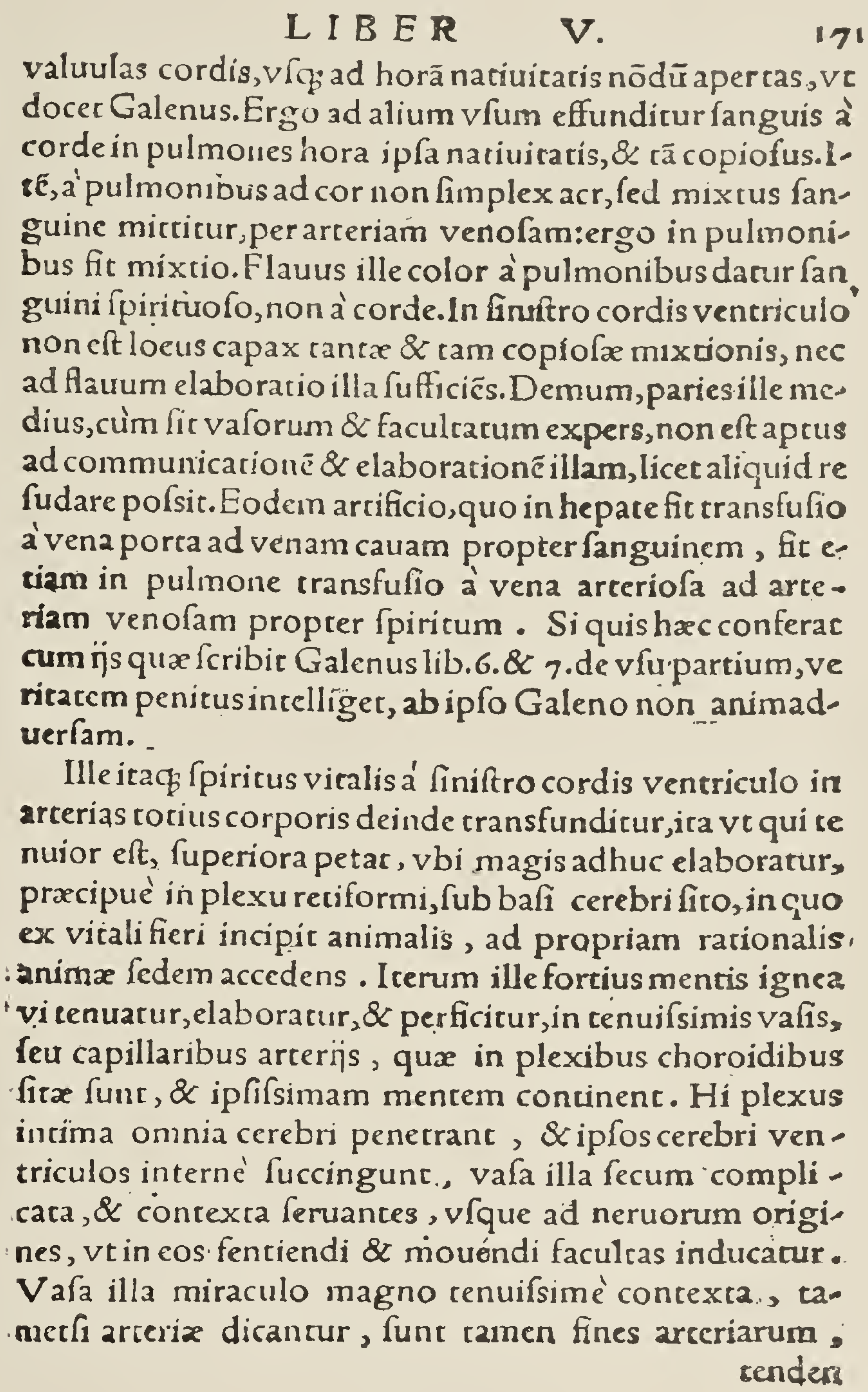


FIG. 10.

Caesalpinus (1569), for whom elaborate claims are made, also knew of the pulmonary circulation, but he thought part of the blood went through the median septum. A more important claim is made for him of the discovery of the general circulation, but it is remarkable that any one knowing the history of the subject could read into his physiology anything more than the old Galenic views.

The history of the circulation bristles with controversy and widely divergent opinions are held as to the merits of the different observers. That Servetus first advanced a step beyond

[3] William Wotton, *Reflections upon ancient and modern learning*, 1697, page 229.

[4] *De re Anatomica Venetiis.*

Galen, that Colombo and Caesalpinus reached the same conclusion independently—all three recognizing the lesser circulation, is quite as certain as that it remained for Harvey to open an entirely new chapter in physiology, and to introduce modern experimental methods by which the complete circulation of the blood was first clearly demonstrated.[5]

A word about the book *Christianismi Restitutio, liber inter rariores longe rarissimus.* Only two complete copies are known, one in the Bibliothèque Nationale, Paris, and the other in the Imperial Library, Vienna, from which I was very kindly permitted to have the photographs of the title-page and the pages describing the circulation of the blood which are here reproduced. A third copy, imperfect, with the first sixteen pages in MS., is in the University Library, Edinburgh. The Paris copy is of special interest, as it belonged to Dr. Richard Mead, the distinguished physician and book collector, by whom it was exchanged with M. de Boze for a series of medals. In 1784 it was secured for the Royal Library. It may now be seen in one of the show cases of the Bibliothèque Nationale, of which it is one of the rare treasures. An added interest is in the fact that on the title-page occurs the name 'Germain Colladon', the Geneva barrister, who prosecuted Servetus; and it is in the highest degree probable that this was the identical copy used at the trial. In one place the book is stained, some suppose by moisture; others think it possible this was the very copy bound upon the victim himself, and snatched from the flames by some one who wished to preserve so interesting a record of the great heretic. The question has been examined carefully by the late Professor Laboubene and M. Hahn, the distinguished librarian of the Paris Faculty of Medicine, both of whom are in favour of fire, not moisture, as the cause of the staining.

In 1791 the Vienna copy was reprinted at Nuremberg in facsimile, page for page, but Dr. de Murr, who was responsible for the reprint, very wisely put the date 1791 at the bottom of the last page. Copies of this edition are not uncommon in the larger libraries. In 1723 Mead attempted to have a reprint made from his copy, but when nearly completed the Bishop of London had it suppressed, and (it is stated) the copies were burnt. A few, however, escaped, and Willis says that he saw one in the library of the London Medical Society. I regret to say that the librarian informs me that this no longer is to be found. A copy of the Mead partial reprint is in the Bibliothèque Nationale, and two copies are in the British Museum.

A last word on the attitude of John Calvin towards Servetus. Much scorn has been heaped upon the great reformer, and one cannot but regret that a man of such magnificent achievements should have been dragged into a miserable heresy hunt like a common inquisitor. Let us not estimate him by his century, as his friends plead, but frankly by his life, and as a man of like passions with ourselves. He had bitter provocation. Flouted for years by the persistent assaults of Servetus, and shocked out of all compassion by his blasphemies, is it to be wondered that the old Adam got the better of his Christian charity? Not only is it impossible to acquit Calvin of active complicity in this unhappy affair, but there was mixed up with it a personal hate, a vindictiveness unbecoming in so great a character, and we may say foreign to it. But let the long record of a self-denying life, devoted in an evil generation to the highest and the best, wipe for all reasonable men this one blot. Let us, if we may judge him at all, do so as a man, not as a demi-god. We cannot defend him, let us not condemn him; let his one grievous fault, even though we may fear he never repented of it, be the shadow which throws into stronger relief the splendid outlines of a noble life. In his defence,[6] the original edition of which I have here, and which is concerned largely with doctrinal questions, not only are there no expressions of regret for the part he played in the tragedy, but the work is filled with insults to his dead enemy, couched in the most vindictive language. On the spot where Servetus was burnt there stands to-day an expiatory monument (Fig. 11), which expresses the spirit of modern Protestantism. On one side is the record of his birth and death, on the other an inscription, of which the following is a translation: 'Duteous and grateful followers of Calvin our great Reformer, yet condemning an error which was that of his age, and strongly attached to liberty of conscience according to the true principles of the Reformation and the Gospel, we have erected this expiatory monument. Oct. 27, 1903.'

The erection next year at Vienna of a quatercentenary monument will complete the recognition by the modern world of the merits of one of the strangest figures on the rich canvas of the sixteenth century. The wandering Spanish scholar, the stormy disputant, the anatomical pro-sector, the mystic dreamer of a restored Christianity, the discoverer of one of the fundamental facts of physiology, has come at last to his own. There are those, I know, who feel that perhaps more than justice has been done; but in a tragic age Servetus played an unusually tragic part, and the pathos of his fate appeals strongly to us.

These, too, are days of retribution, of the restoration of all things, the days of the opening of the fifth seal, when the souls under the altar see their blood avenged, when we clothe in the white robes of charity those who were slain for the testimony which they held, little noting whether the martyr was Catholic or Protestant, caring only to honour one of that great company which no man can number, 'whose heroic sufferings,' as Carlyle says, 'rise up melodiously together to heaven out of all lands and out of all time, as a sacred Miserere, their heroic actions also as a boundless everlasting Psalm of Triumph.'

Note.—The Servetus bibliography is fully given to 1890 in Professor A. V. D. Linde's *Michael Servetus*, Groningen, 1891. My personal interest dates many years back when Pastor Tollin's delightful sketches enlivened the numbers of Virchow's *Archives.* No one has ever had a more enthusiastic biographer, and to the writings of the Madgeburg clergyman we owe the greater part of

[5] John C. Dalton's *History of the Circulation*, 1884, gives by far the best and fullest account of the whole subject in English.

[6] *Defensio Orthodoxae, &c.*, 1554.

our modern knowledge of Servetus. The best account in English is by Willis—*Servetus and Calvin*, 1877. A German translation of the *Christianismi Restitutio* by Dr. Bernhard Spiess appeared in 1895 (2nd edition, Wiesbaden, Chr. Limbarth). I am indebted to Professor Harper of Princeton for an historical drama, *The Reformer of Geneva*, by Professor Shields (privately printed, Princeton University Press, 1897), which gives an admirable picture of Geneva at the time of the trial. From Chéreau's *Histoire d'un Livre*, 1879, I have 'cribbed' the idea of the introduction. The name of Mosheim must be mentioned, as his writings were for years the common tap from which all Servetus knowledge was derived. The Servetus portrait, of which Mosheim speaks, has disappeared; I have reproduced the engraving from Allworden's *Historia* (1727), also the Roch statue at Anamnese.

REMARKS ON THE OCCASION OF THE DEDICATION OF THE NEW HALL OF THE COLLEGE OF PHYSICIANS OF PHILADELPHIA.

By WILLIAM SYDNEY THAYER, M. D.,
Associate Physician, The Johns Hopkins Hospital, Baltimore.

To bring the greetings of the Medical and Chirurgical Faculty of Maryland to its older sister, The College of Physicians of Philadelphia is an honor and a pleasure. But perhaps, after all, 'tis not as a sister that it should greet you but rather as a child. For a large number, more than a quarter of the one hundred and one founders of our Faculty gained their inspiration in Philadelphia from study with men who were founders or members of this honorable institution. And from that day to to this, we in Maryland have ever sought refreshment from the quickening current which has flowed from the lips of your students and philosophers and poets.

Among the charter members of our Society was John Archer who, in the year 1768, received from the College of Medicine of Philadelphia the first medical diploma awarded in America after a course of study; and 'tis a significant fact that in the one hundred and ten years of the life of our Society nearly one-half of its honorary members have received their medical education in Philadelphia.

In another sense 'tis with a feeling of peculiar pride that one enters the abode of this most distinguished and representative body. Nowhere has the physician, from the beginning, occupied so important a position in the community as here. In the past the title Doctor of Medicine has had, in many regions, an humble significance. In Philadelphia, however, from the earliest times, the social sphere of the physician has been larger and fuller than in almost any other spot in the world; and few, if any cities can point, among the annals of their practitioners and teachers and students, to so long a line of men of broad general culture, who have not only contributed to the advance of the science and art of medicine, but have been scholars in a larger sense and true leaders of men.

Here in Philadelphia more than in almost any other city, physician has been synonymous with gentleman and scholar. And who more exemplifies what the physician may be, how many sided and diverse may be his interests and his influence, in science, in culture and in letters, than your honored member to whose fine words we listened but a few months ago in Osler Hall?

The foundation of a body such as this in 1787 is a striking evidence of the character of the medical profession in Philadelphia over one hundred and twenty years ago. How much this college has done to elevate and uphold the standards of medicine needs no comment.

The library early became an important feature of your organization and the influence which this admirable collection has had upon medicine not only in this city but in the country at large, is not to be overestimated. Next to the Surgeon General's Library, this institution is probably mainly to be thanked for a most honorable and I think one of the most characteristic features of the better American Medical Literature. I refer to that broad familiarity shown, almost always, by the investigator with the contributions to literature of students from all parts of the world. The facilities offered for the study of the original communications of foreign authors by the accumulation of libraries such as this, and especially by the establishment of that inestimable blessing the Surgeon General's Library, have been of incalculable benefit to American medicine. It is largely through the opportunities afforded by these institutions and through the foundation of the Index Catalogue and the Index Medicus, that the American student has learned so well how and where to seek for the literature upon any question in which he is interested; and this knowledge and these opportunities have gone far toward delivering us from vain contentions as to priority as well as from that medical Chauvinism which is so dangerous an enemy of the cause of truth.

At one of the earliest meetings of this college Benjamin Rush speaks thus of the benefits which may follow its foundation: "By stated meetings as a college we may promote enquiries and observations upon the prevailing diseases of the city. Here the timid may be encouraged and the sanguine may be taught to doubt." (What a happy phrase!) "Here the young practitioner may profit by the experience of the old, and the old by the boldness of enquiry, and modern improvements of the young. Here uniformity in principle and practice in medicine will gradually insinuate themselves. Nor will the advantages of our conferences end in the acquisition of knowledge. The heart will naturally interest itself in the pursuits of the head. Here friendships will be contracted and cemented, and occasional and unavoidable suspicions or disputes may be accommodated by explanation or mediation. By these means we shall become not only the

guardians of the honor of the profession, but likewise of each other's character."

What words could better describe the advantages of a college of physicians! How well have the hopes of the speaker been fulfilled!

What the physician was so early in this community, what this college has helped him to be in the century which has passed, that he is coming to be all over the world to-day.

Bound by no "human creed," by no blinding faith or prejudice of tradition, given over wholly to the search for truth and its application to the promotion of the welfare of mankind, no human interest is foreign to the true physician. A broad sympathy born of a knowledge of the errors of the past and a full appreciation of the will-o'-the-wisps that beset us to-day, a devotion to the cause of justice and liberty, a tolerance full of pity for ignorance and the ills moral and physical which it bears, a hatred of superstition and intolerance and an abhorrence of all influences which fetter or pervert the free moral and intellectual development of his fellow, these are sentiments which must animate and guide him who devotes his life to the search for truth. And so it has come to pass that the physician who, in the past, was too often the humble servant of the ruling influences in the community, social, political, religious, occupies to-day a position in the front rank not only of the army of students of the natural sciences, but of every great movement for liberty, for justice, for the elevation and emancipation of the masses—careless as ever of his life in the presence of pestilence, or of his worldly reputation in the face of entrenched prejudice and intolerance. What wonder is it that men whose lives are given over to such ideals should become leaders as well as servants of mankind! What wonder is it that among them there should develop now and again the rare powers of imagination and expression which mark those great physicians whom we call poets! What wonder is it that out of our body should come a Holmes and a Weir Mitchell!

This college has been in the past one of the noblest nurseries of searchers for truth, of men who have followed consistently the wise admonition of our poet:

> Take from the past the best its toil has won,
> But learn betimes its slavish ruts to shun.
> Pass the old tree whose withered leaves are shed,
> Quit the old paths that error loved to tread,
> And a new wreath of living blossoms seek,
> A narrower pathway up a loftier peak;
> Lose not your reverence, but unmanly fear
> Leave far behind you, all who enter here!

May it ever serve to broaden and extend the horizon of the physician, to stimulate his love of beauty and truth and justice and liberty and tolerance, to bring him nearer to his fellow man, to give to the world wise and fearless counsellors and leaders!

THE METHOD OF ZADIG IN MEDICINE.[1]

By M. G. Seelig, M. D., of St. Louis.

In 1747, Voltaire wrote a series of tales entitled, "Zadig Or Destiny—An Eastern Tale," the burden of the small volume of twenty-one chapters being to prove the value of proper observation and correlation of facts. The historical identity of Zadig himself, seems to be about as accurately fixed as is the geographical situation of Shakespeare's Forest of Arden, for the only data at command concerning the life action of the man are the unverified statements of Voltaire himself. And yet, withal, the great Cuvier saw fit to characterize a particularly strong bit of evidence as, "une marque plus sûre que toutes celles de Zadig."

It was in the year of 837 of the Hegira, that a certain Sadi sent to the Sultan Sherah an epistle, introducing the book of Zadig, saying that it was written originally in the ancient Chaldee, and then translated into Arabic, at about the time that the Persians and Arabians were beginning to compose the Thousand and One Nights. Zadig is introduced as a young man, living in Babylon, during the reign of King Moabdar. Huxley, in his essay on Zadig tells us that he was not able to find any mention of Moabdar in the list of Babylonian sovereigns, so carefully worked out by modern students of the old cuneiform inscriptions. All this however, in the language of Kipling, is another story. Authenticated, or unauthenticated, we have the word of the Sadi, that Zadig was young, rich, unpretentious, respectful, restrained in passion, generous in his judgment of others, and educated in all the sciences of the ancient Chaldeans. Swayed by the same passions that move the modern youth, he was forced through the direct and indirect results of unfortunate love affairs, into retirement from the world of people, and had his energies directed toward the world of things. The fair Semira was his first love. Orcan, a deadly rival, made a bold attack on the lovers, wounding the lady slightly, but injuring Zadig so seriously, that Hermes, the great physician of Memphis was called to attend him. Hermes found an injury of the left eye, and prognosticated not only abscess formation, but even foretold at what hour and minute the sight of the eye would be lost. While all Babylon was still wondering in admiration at the great skill of Hermes, the abscess broke, resulting in a complete spontaneous cure of Zadig. Hermes later wrote a book, proving that by all the laws of science, a cure should *not* have occurred. Semira, in the meantime, trusting the prognostic skill of Hermes, had eloped with the rival Orcan, in order to escape the fate of marrying a one-eyed man. Rendered wise by his experience, Zadig put his next love, Azora, to a cleverly planned test, before marrying

[1] Read before the Medical History Club of St. Louis, Mo., Oct. 28, 1909.

her. This damsel also fell from grace, and Zadig, disheartened, retired to the banks of the Euphrates, seeking happiness in the study of nature. His parting shot, before retirement was in the shape of an epigram to the effect that married life was divisable into two parts, one part the moon of honey, and the other part, the moon of wormwood. Once settled in quiet and solitude, he studied the properties of animals and plants so assiduously, that he acquired a sagacity enabling him to see a thousand differences, where other men saw uniformity.

As illustrative of the keenness of Zadig, we have the following excerpt taken from Voltaire's work:

One day, walking near a little wood, he saw hastening that way, one of the Queen's chief eunuchs, followed by a troop of officials, who appeared to be in the greatest anxiety, running hither and thither, like men distraught, in search of some lost treasure.

"Young man," cried the eunuch, "have you seen the Queen's dog?" Zadig answered modestly, "A bitch, I think, not a dog." "Quite right," replied the eunuch; and Zadig continued, "A very small spaniel who has lately had puppies; she limps with the left fore leg, and has very long ears." "Ah! you have seen her then," said the breathless eunuch. "No," answered Zadig, I have not seen her; and I really was not aware that the Queen possessed a spaniel."

By an odd coincidence, at the very same time, the handsomest horse in the King's stable broke away from his groom in the Babylonian plain. The grand huntsman and all his staff were seeking the horse with as much anxiety as the eunuch and the people the spaniel; and the grand huntsman asked Zadig if he had not seen the King's horse go that way.

"A first rate galloper, small hoofed, five feet high; tail three feet and a half long; cheek pieces of the bit of twenty-three carat gold; shoes silver?" said Zadig.

"Which way did he go? Where is he?" cried the grand huntsman.

"I have not seen anything of the horse, and I never heard of him before," replied Zadig.

The grand huntsman and the chief eunuch made sure that Zadig had stolen both the King's horse, and the Queen's spaniel, so they haled him before the high court of Desterham, which at once condemned him to the knout, and to transportation for life to Siberia. But the sentence was hardly pronounced, when the horse and spaniel were found. So the judges were under the painful necessity of reconsidering their decision; but they fined Zadig four hundred ounces of gold, for saying that he had seen that which he had not seen.

The first thing was to pay the fine; afterward Zadig was permitted to open his defense to the court, which he did in the following terms: "Stars of justice, abysses of knowledge, mirrors of truth, whose gravity is as that of lead, whose inflexibility is as that of iron, who rival the diamond in clearness, and possess no little affinity with gold; since I am permitted to address your august assembly, I swear by Ormuzd that I have never seen the respectable lady dog of the Queen, nor beheld the sacrosanct horse of the King of Kings. This is what happened. I was taking a walk toward the little wood near which I subsequently had the honor to meet the venerable chief eunuch and the most illustrious grand huntsman. I noticed the track of an animal in the sand, and it was easy to see that it was that of a small dog. Long faint streaks upon the little elevations of sand between the footmarks convinced me that it was a she dog with pendant dugs, showing that she must have had puppies not many days since. Other scrapings of the sand, which always lay close to the markings of the forepaws, indicated that she had very long ears; and as the imprint of one foot was fainter than those of the other three, I judged that the lady dog of our august Queen was, if I may venture to say so, a little lame."

"With respect to the horse of the King of Kings, permit me to observe that, wandering through the paths that traverse the wood, I noticed the mark of horse shoes. They were all equidistant. Ah! said I, this is a famous galloper. In a narrow alley, only seven feet wide, the dust upon the trunks of the trees was a little disturbed at three feet and a half from the middle of the path. This horse, said I to myself, has a tail three feet and a half long, and, lashing it from one side to another, he has swept away the dust. Branches of the trees met overhead, at the height of five feet, and under them, I saw newly fallen leaves; so I knew that the horse had brushed some of the branches and was, therefore, five feet high. As to his bit, it must have been of twenty-three carat gold, for he had rubbed it against a stone which turned out to be a touchstone, with the properties of which I am familiar by experiment. Lastly, by the marks which his shoes left upon pebbles of another kind, I was led to think that his shoes were of fine silver."

All the judges admired Zadig's profound and subtile discernment; and the fame of it reached even the King and Queen. From the anterooms to the presence chamber, Zadig's name was in everybody's mouth; and although many of the magi were of the opinion that he ought to be burned as a sorcerer, the King commanded that the four hundred ounces of gold which he had been fined be restored to him. So the officers of the court went in state with the four hundred ounces; only they had retained three hundred and ninety-eight for legal expenses, and their servants expected fees.

Thus are we furnished with the basis of the fundamental conception of Zadig's method. Whether Zadig himself ever existed in the flesh, or whether he was a mere figment of Voltaire's imagination, it is not our concern; nor is the unhappy spirit of pessimistic philosophy which he later developed, and in which he enveloped himself, of more than passing interest, in a biographical way. Our purpose lies much deeper than that of mere raconteur, for these stories of the method of Zadig hold within themselves a text of interest to every thinking medical man, and open anew the whole question of the comparative merit of deductive and inductive processes of thought, in establishing medical facts.

One might quote from the pages of medical history, to show that Zadig, with all his cleverness in inductive reasoning was preceded hundreds of years, by men who applied exactly the same method to unravelling the symptoms of disease.[2] Or adopting the plan of Huxley (3), Lauder Brun-

[2] Erasistratus, three hundred years before Christ, was called upon to treat Antiocus, the son of Seleukus, King of Syria. The boy had wasted to a skeleton, and was in a dying condition, despite the fact that no demonstrable organic lesion could be made out. Erasistratus noted that whenever the wife of the king visited the sick chamber, the patient's pulse became rapid and irregular, his face flushed, his voice halting, weak, and faltering, and his skin moist with perspiration. When she left the room, the patient became pale and anxious. The young and beautiful queen was the second wife of the old king, and consequently, the stepmother of the sick prince. Erasistratus reached the conclusion from all this data, that the prince was lovesick for his stepmother, and pointed out to old Seleukus the only rational way of curing the supposedly fatal malady of the prince. Seleukus, following the counsel offered him, proved the correctness of Erasistratus' induction (1). In a very similar fashion, the Arabian physician, Dschibrail, concluded that the favorite wife of the Caliph was

ton (4), and Balfour (5), numerous instances might be gathered from the modern sciences, demonstrating Zadig's method to be the basis of many of the greatest discoveries in science. We might even quote the modern vogue of the Sherlock Holmes method of thought, in order to emphasize the present day confirmation of inductive autocracy. But, to adopt any one of these courses without due qualification, would mean placing a crown on the brow of induction, and at the same time declaring an interregnum, in the realm of deduction. It would mean the utterance of an unqualified statement, such as Leube makes in the introduction to his masterly work, *Diagnose der inneren Krankheiten:* "Um ueber die bestimmte Form einer Krankheit im Gegebenen Fall ins Klare zu kommen, ist der einzig richtige Weg der fuer die Erforschung von Naturobjecten, ueberhaupt seit Francis Bacon zur Geltung gekommene, die Anwendung der Induction." To such an affirmation, we are not prepared to subscribe.

If we may judge from battles waged before, entrance of this sort upon the field of the comparative merits of philosophical thought, is a bold move; intrepid indeed, if our purpose were a bona fide attempt to solve the problem. It is well, therefore, to express early, the sentiment that a decision regarding the one perfect method of reasoning is not attempted. Such a decision must eventually be left to the dialectic philosophers; dialectic philosophy has no place in medical reasoning. Possibly, it was this very truth, which prompted Osler to refer to Minerva Medica as hating philosophy with a deadly hatred. Be all this as it may, however, the fact remains that medical thought is *thought*, and must needs obey the abstract laws of thought as rigidly as do the heavenly bodies the laws of gravity. Conscious or unconscious conformity to the laws of logic means right thinking, nonconformity, wrong thinking. It is not entirely without interest and profit therefore, to examine the various methods of thought, and to determine for ourselves whether the glamor of the method of Zadig shall ensnare us, whether the authority of a Leube shall command us, or whether, after all, though unskilled in the intricate and abstract methods of reasoning, we may not still be able to estimate comparative values.

For our purposes, we may regard deduction as a process of thought which determines a fact by establishing its fixed relationship to a general law; induction as a process of thought which determines a general law by establishing its fixed relationship to a large number of correlated facts. The stock in trade of deduction lies in the possession of a general law, the profit of the transaction being a new fact; conversely, in induction, the working capital is made up of numerous facts, the profit being the development of a new general law. "Deduction reasons from principles, induction reasons to principles." Pasteur, by careful experimentation, and by the equally careful notation of resulting phenomena, induced his celebrated theory of germs. Lister, accepting as proved, the general law laid down by Pasteur, deduced the single fact that a wound would heal by primary intention, provided the entrance of germs be barred. Here then, in essence, is a statement of the methods. In substance, the matter is not so simple. The logicians and metaphysicians have fogged the subject for us by the introduction of a complicated nomenclature, compromise terms, discussions concerning priority of discovery of the inductive method, and numerous complex, abstruse argumentations which we must of necessity leave out of consideration, if we entertain the slightest hope of skirting the treacherous circle of hopeless ratiocination. A consideration of the claims that have been advanced for daVinci, Cesalpinus, Copernicus, Roger Bacon and others, as the father of the inductive method, a critique on the Hume-Kant controversy regarding the account of causation, or an attempt to untangle the snarl of arguments holding within their meshes all the abstractions of "necessary connection," "invariableness," "concomitant variation," and "perfect and imperfect induction," would lead us where?

The centipede was happy quite,
  Until the toad, for fun,
Said, "Pray, which leg comes after which?"
This wrought his mind to such a pitch,
He lay distracted in the ditch,
  Considering how to run.

Is then the matter, after all, so complicated? Are we, ordinary individuals, poorly schooled in the intricacies of the fundamental laws of thought and reasoning, apt, at any moment, to stultify ourselves by stating conclusions drawn from faultily constructed premises? By no means. Man's power to think rationally is an heritage, bequeathed to him, as a result of countless ages of evolution; "the unconscious logic of common sense," Huxley calls it. The novel point of view asserted by Buckle (6) lends weight to the epigram of Huxley. Buckle believes that tradition and environment play such important parts in the evolution of man's method of thought, that certain lands will show a preponderance of thinkers who reason deductively, and other countries a preponderance of thinkers who follow the inductive method.[3]

It is not overstating the point, to say that man's power to think well, varies within limits as broad as those of his power

suffering from a hysterical paralysis of the arms; and proved the correctness of his method of reasoning by attempting suddenly to raise the skirts of the patient, who in a frenzy of modesty, repelled him with the two arms that, only a moment before had been totally paralytic (2).

[3] Buckle selects John Hunter to exemplify the effect of environment on thought processes, and states that during the time Hunter made Scotland his home, his reasoning was confined within narrow deductive limits (Buckle carefully developed the idea that Scottish thought was inherently deductive), whereas later, in the freer air of England, he reasoned almost exclusively inductively.

It is interesting to note how universal is the tendency to associate the name and work of Hunter with the manner in which he reasoned. His biographers dwell at length upon the subject, and the various Hunterian orators rarely fail to devote a large part of their orations to the relationship between logic and medicine. (See, for example, the oration by Henry Morris (7) and John Tweedy (8).)

to digest well, or to move gracefully. Sound thought, normal digestion, and pleasing grace, all may be cultivated equally well, without intimate knowledge of logic, enzymes, or muscular action. Taine tells us, that in 1685, in the great hall of Dublin, the professors were engaged in examining for the bachelor's degree a poor scholar, awkward, friendless, and carrying the onus of having failed to take his degree once before, on account of his ignorance of logic. When the argumentation came on, the student was unable to reduce his replies to syllogism, and when he was asked how he could hope to reason well with a knowledge of the rules of reason, he replied, that he *did* reason pretty well without them. In pity, and with smiles of lament for his feeble brain, the examiners passed the scholar—who was none other than Jonathan Swift.

Swift did not misstate the truth, for, indeed, man may reason "pretty well," without a knowledge of rules, just as he may reason pretty badly, by use of them. The value of the method of Zadig, as applied to medicine lies not in that a fact of general import is drawn from numerous detailed observations; but rather in the emphasis that the method lays on the importance of careful, detailed observation, and a clear conception of cause and effect. Leube should have recommended, for purposes of medical diagnosis, the qualities of keen observation, correct inference, and sound judgment, rather than any particular type of syllogistic reasoning; for the mind of man can be hemmed in by syllogisms no more than his body form can be limited by the laws of artistic proportion.

It is strange, this insistence that the medical man must confine himself to rockribbed facts, and shun all a priori unproved theories; and yet, withal, not so strange, when we consider that the doctrine dates from Francis Bacon's announcement that man must not impose his own preconceptions ("anticipationes menti") on nature. Such a doctrine presupposes that man can, at will, make a tabula rasa of his mind, can at command blot out the countless thousands of stimuli that constantly pour in through his organs of sense, each stimulus possessing the latent power of suggesting a new law, and therefore serving as the basis for an a priori deduction. Pasteur did not toilsomely confirm and reconfirm, by experiments, to find in the end, that he was able to induce the law of germs. The law was first conceived by his fertile brain as an a priori possibility, and then confirmed, inductively, by carefully planned experiments. The even greater discovery, by Robert Mayer, of the conservation of energy, grew out of the a priori assumption that "causa aequat effectum." And Darwin tells us that fifteen years before he was ready to induce his great conclusion, from stack upon stack of isolated facts, he had conceived the theory that favorable variations would tend to be preserved, and unfavorable ones to be destroyed. Indeed, his enthusiasm was not aroused to the fullest extent, until, as he says, "Here, then, (in Malthus' views on population) I had at last got a theory, by which to work" (9).

The examples of Pasteur, Mayer, and Darwin are cited merely to emphasize the fact that induction and deduction are partners, in practically all generalized instances of thought processes. The two methods are not hostile, as we might be led to infer from many of the writings on this subject, but supplementary. Surely Huxley was not unmindful of this fact, when he glorified Zadig and his method; for ten years before he wrote the essay on Zadig, pointing out the importance of the inductive method to science, he wrote an essay (On Descartes' Discourse Touching the Method of Using Ones Reason Rightly and of Seeking Scientific Truth), commemorating him who had vitalized the doctrine of "Cogito, ergo sum," and who stands as the archtype of the champions of the deductive method—Réné Descartes. Furthermore, in one of his later essays (Progress of Science) Huxley clearly states that results in science depend not upon method of thought, but rather upon the "divine afflatus of the truth seeker," not upon the direction in which the mind is "intended," but upon the mind itself.

And so, in the end, there is left just a word to be said, a word of commendation, not only for the inductive method of Zadig, which when properly used, trains the senses to observe, and the mind to infer; but also for the method of deduction, which teaches the value both of hearkening to a priori thoughts and theories, and of attempting to confirm or negate them. The assumptions that constantly knock for admission to the consciousness of the medical mind are the fairy tales that preserve youth, by strengthening imagery; and surely if the medical man is not to become a medical automaton, he must imagine, he must theorize. In thought, as in action, he must at times be patient, cautious, and creeping, after the fashion of the inductive method, but at other times bold, dexterous, and even rash, after the manner of the deductive. Claude Bernard (10) used to say, "Put off your imagination, as you take off your overcoat, when you leave the laboratory. Before the experiment, between whiles, let it wrap you around; put it right away from yourself during the experiment itself, lest it hinder your observing power."

Note.—Literature does not contain a more artistic dissection of the medical mind than that furnished by Taine (11) in his account of Sir Thomas Browne: "It is just the poet's imagination which urges him onward into science. Face to face with the productions of nature he abounds in conjectures, comparisons; he gropes about, proposing explanations, making trials, extending his guesses like so many flexible and vibrating feelers into the four corners of the globe into the most distant regions of fancy and truth. As he looks upon the tree-like and foliaceous crusts which are formed upon the surface of freezing liquids, he asks himself if this be not a regeneration of vegetable essences dissolved in the liquid. At the sight of curdling blood or milk, he inquires whether there be not something analogous to the formation of the bird in the egg, or to that coagulation of chaos which gave birth to our world. In presence of that impalpable force which makes liquids freeze he asks if apoplexy and cataract are not the effects of a like power, and do not indicate also the presence of a congealing agency. He is in presence of nature as an artist, a man of letters in presence of a living countenance, marking every feature, every movement of physiognomy, so as to divine the passions and the inner disposition, ceaselessly correcting and undoing his interpretations, kept in agitation by thought of the invisible forces which operate

beneath the visible envelope. The whole of the middle ages and of antiquity, with their theories and imaginations, Platonism, Cabalism, Christian theology, Aristotle's substantial forms, the specific forms of the alchemist—all human speculations, entangled and transformed one within the other, meet simultaneously in his brain, so as to open up to him vistas of this unknown world. The accumulation, the pile, the confusion, the fermentation and the inner swarming, mingled with vapors and flashes, the tumultuous overloading of his imagination and his mind, oppress and agitate him. In this expectation and emotion his curiosity takes hold of everything; in reference to the least fact, the most special, the most absolute, the most chimerical, he conceives a chain of complicated investigations, calculating how the ark could contain all creatures, with their provision of food; how Perpenna, at a banquet, arranged the guests so as to strike Sertorius; what trees must have grown on the banks of Archeron, supposing that there were any; whether quincunx plantations had not their origin in Eden, and whether the numbers and geometrical figures contained in the lozenge-form are not met with in all the productions of nature and art. You may recognize here the exuberance and the strange caprices of an inner developement too ample and too strong. Archæology, chemistry, history, nature—there is nothing in which he is not passionately interested, which does not cause his memory and his inventive powers to overflow, which does not summon up within him the idea of some force, certainly admirable, possibly infinite. But what completes his picture, what signalizes the advance of science, is the fact that his imagination provides a counterbalance against itself. He is as fertile in doubts as he is in explanations. If he sees a thousand reasons which tend to one view, he sees also a thousand which tend to the contrary. At the two extremities of the same fact, he raises up to the clouds, but in equal piles, the scaffolding of contradictory arguments. Having made a guess, he knows that it is but a guess; he pauses, ends with a perhaps, recommends verification. His writings consist only of opinions, given as such; even his principal work is a refutation of popular errors. In the main, he proposes questions, suggests explanations, suspends his judgments—nothing more. But this is enough: when the search is so eager, when the paths in which he proceeds are so numerous, when it is so scrupulous in securing its hold, the issue of the pursuit is sure; we are but a few steps from the truth."

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DR. LEMUEL HOPKINS, ONE OF THE CELEBRATED HARTFORD WITS, AND A FORGOTTEN, DISTINGUISHED AMERICAN STUDENT OF TUBERCULOSIS.

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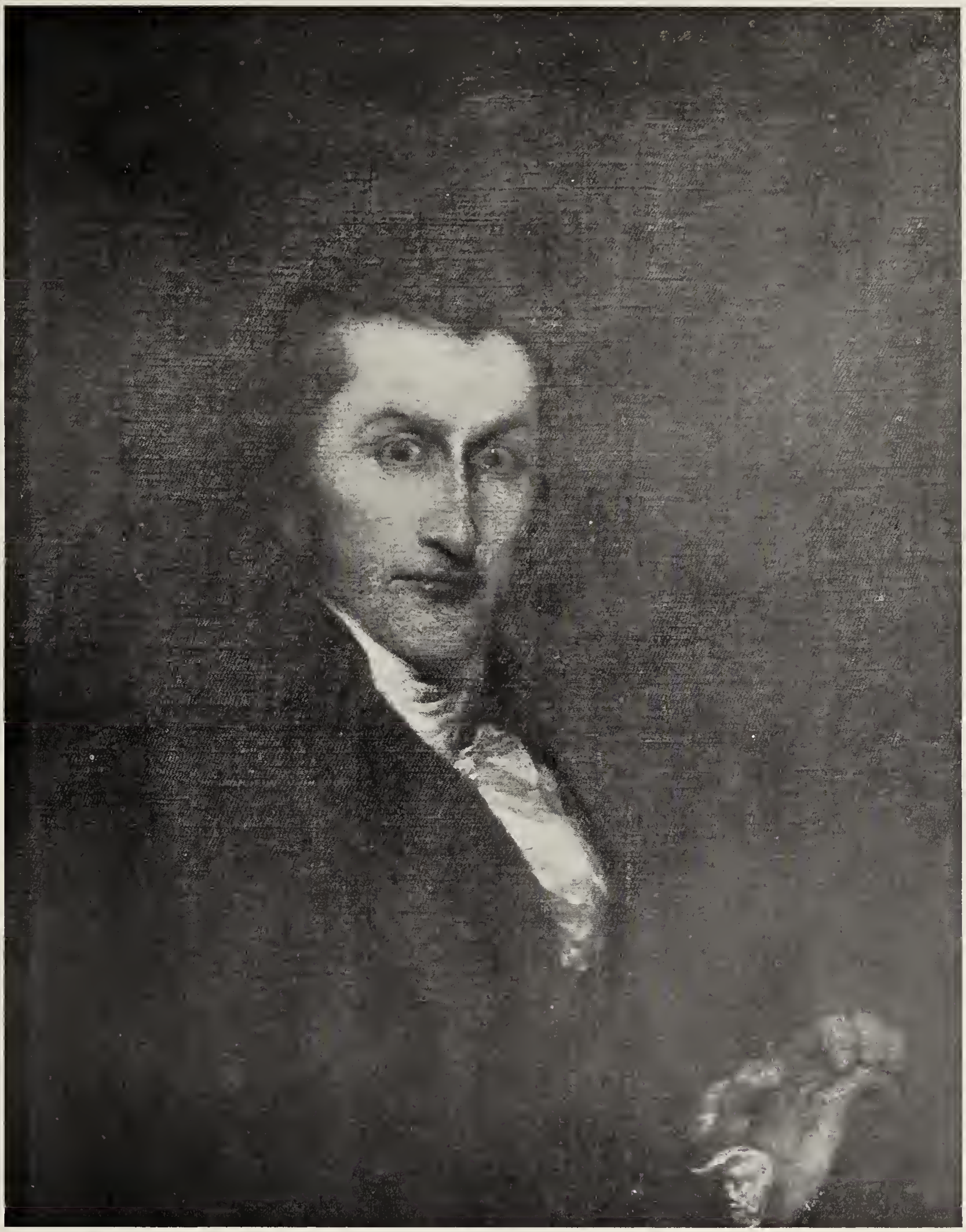
When the trying days of the Revolution were over, Hartford became the Mecca for a little band of kindred literary spirits, who formed themselves into a "friendly club" and were subsequently known as the Hartford Wits. Thus the center of our literary activity, in that time, became located in Hartford. The club was accustomed to hold weekly meetings to discuss political and philosophical subjects, and was composed of members, who then enjoyed extensive reputations. They were: John Trumbull, a lawyer, whose political satire on Toryism, M'Fingal, was widely read during the Revolution and in the years immediately following; Timothy Dwight, not a resident of Hartford, yet a member of the group, famous as Yale's President and as a preacher of righteousness; David Humphreys, faithful as a soldier and diplomat, to be remembered on account of Washington's friendship for him; Joel Barlow, a perfunctory chaplain during the Revolution, a newspaper editor, an unsuccessful lawyer, a man of letters and finally our minister to France; Theodore Dwight, a newspaper editor, a Congressman and Secretary of the Hartford Convention; Richard Alsop, a man absorbed in literature and one proficient in many languages; and Lemuel Hopkins, popular as a general practitioner and as a consultant, of especial renown in his treatment of tuberculosis, a physician with a keen, dry biting wit. To these have been added Dr. Elihu H. Smith, fervent in his love of literature and in his desire to elevate his chosen profession, and Dr. Mason F. Cogswell, a man of parts as a surgeon and indefatigable in his efforts to found a school in this country for the deaf and dumb. He was the first in America to ligate the common carotid. But the two last named played only a minor part in the productions of the Hartford Wits, being the authors of a few lines in the Echo, but not assisting in the Anarchiad or the Political Green House, the other products of this group.

No set of men ever showed a greater admiration for one another. Trumbull, who was considered as their leading representative, is variously referred to by them. In Barlow's works[1] we find the lines: "See! Trumbull leads the train;"

[1] The vision of Columbus, Hartford, 1787, p. 211.



Yours sincerely
Leml Hopkins

Photograph of a portrait of Dr. Lemuel Hopkins. The original portrait was painted by John Trumbull, in 1793. The copy, from which this photograph was made, was painted by Trumbull in 1825, for Samuel Miles Hopkins, and is now in the possession of the family of the late Dr. George G. Hopkins, of Brooklyn. I am indebted to his son, Dr. Joseph Gardner Hopkins, for this photograph.

in Dwight's poems:[2] "Trumbull leads the ardent throng;" in Humphrey's poems:[3] "Trumbull! earliest boast of fame;" and in Alsop's poems:[4] "Lo Trumbull wakes the lyre." Dwight is given numerous titles, *e. g.*, Majestic Dwight, sublime in epic strain (Alsop),[5] blest Dwight (Humphreys)[6] and Dwight of Homeric Fire (Trumbull).[7] Barlow is dubbed a child of genius by Humphreys,[8] while Alsop[9] speaks thus of him:

> . . . . in Virgilian Barlow's tuneful lines
> With added splendor great Columbus shines.

Humphreys is said to be "in lore of nations skilled and brave in arms (Barlow).[10] Hopkins[11] also showed his affection for the members of this group by writing thus to Barlow who had then left Hartford: "Hartford has become a very different place to me since you and friend Walcott left it, and, Trumbull apart, has no more charms for me than Muskingmum." Elsewhere[12] he writes "Trumbull will, I fear, within a year or two, quit 'the visible diurnal sphere.' What, then, O Hartford, hast thou for me? Pleasant indeed shalt thou remain, but chiefly for the joys that are past."

But the member of the Hartford Wits, who more particularly concerns us, was Dr. Lemuel Hopkins. He was born in the Salem society (now Naugatuck) on June 19, 1750, being the second son of Stephen Hopkins, Jr., and Patience, his second wife.[13] Of his boyhood we know nothing, save that he was of a slender constitution and was then troubled with a "cough, hoarseness, a pain in the breast and the spitting of blood."[14] "On his mother's side" he "was descended from a consumptive parent and family,"[15] and he had "that form of body which had been long observed to indicate a predisposition to consumption."[16]

After being given a good classical education by his father, who was a farmer in easy circumstances, he began the study of medicine under the distinguished Dr. Jared Potter, of Wallingford. Subsequently he removed to Litchfield and placed himself under the instruction of Dr. Seth Bird. In 1776 he began the practice of medicine in that town and served for a short time, during this year, as a volunteer soldier in the Revolutionary Army. While acting in this latter capacity, he is said to have shown his strength by firing a king's arm held in one hand, with arm extended at full length—a feat which the other participants, a number of officers, had attempted in vain.[17] From Litchfield he removed to Hartford, in 1784, where he resided, from 1790 until his death, in a house which he had bought from Captain William Bull. It was situated on the west side of Main Street, a little south of the corner of Church. I have been unable to locate Mr. William Limon's house, in which he appears to have lived until 1790.[18]

It is a matter of much regret that we have but little to give of his life's history. His printed poems, some scanty memoirs, which include many anecdotes concerning him, and a few of his letters have already appeared in print, but his manuscript treatise on consumption, which Thacher's Medical Biography[19] says is "too valuable to be lost," and his manuscript treatise on colds have remained concealed until now. With this material, with ten unpublished letters in the Walcott Collection, at the Connecticut Historical Society, and seven more in the possession of the Connecticut State Medical Society, as well as with the Manuscript memoir by his nephew, Samuel Miles Hopkins, we shall endeavor to give some estimate of his character and accomplishments.[20]

Joel Barlow had preceded Hopkins to Hartford by about a year. Where they had previously met is uncertain, but a warm friendship had sprung up between them, as is evinced by Hopkins' staying at Barlow's house until he could find a resting place for himself in Hartford. In a letter to his brother-in-law, Hopkins thus speaks of his removal: "Though the clouds, wind and stars fought against us, yet Goods and Family arrived safe in Port, in due time. The goods came in yesterday about eleven o'clock—the family in the beginning of the evening. We unloaded at Mr. Limon's, but I am not sure we shall live there till he leaves the House. However I believe we shall live somewhere on one side or the other of the un-equinoxial line of Death; and I do not much care where, or on which side said line, provided I have my Friends about me. But the Waggoner has arrived (I mean at Mr. Barlow's, where I forgot to tell you we put in for the present, tho' they have but half a house: for each good author is as good as a friend) and I must stop short to send him away."[21]

Practice may have been slow at first, for we find Hopkins had some intentions of removing to New York. On December 2, 1789, he adds the following, in a postscript, to a letter to Oliver Walcott: "I have had several talks with Captain Watson. He expressed a desire that I should move to New York, and tho' aware of the real difficulties, which might

[2] The Miscellaneous Works of Colonel Humphreys, New York, 1790, p. 109.

[3] Ibid, p. 54.

[4] The Charms of Fancy, New York, 1856, p. 47.

[5] Ibid.

[6] The Miscellaneous Works of Colonel Humphreys, loc cit.

[7] The Poetical Works of John Trumbull, Hartford, 1820, II, p. 109.

[8] The Miscellaneous Works of Colonel Humphreys, New York, 1790, loc. cit.

[9] Loc. cit.

[10] Loc. cit.

[11] Todd, Life and Letters of Joel Barlow, New York, 1886, p. 112.

[12] Marble, Heralds of American Literature, Chicago, 1907, p. 142.

[13] Anderson's History of Waterbury, New Haven, iii, p. 927.

[14] MSS. Treatise on Common Cold or Catarrh.

[15] Ibid.

[16] Ibid.

[17] Russell, Early Medicine and Early Medical Men in Connecticut. Proc. Conn. Med. Soc., Bridgeport, 1892, p. 152.

[18] MSS. letter in possession of the Conn. State Medical Society.

[19] Thacher, American Medical Biography, Boston, 1828, I, p. 303.

[20] He was made an honorary member of the Massachusetts Medical Society in 1791 and seven years earlier had received the honorary degree of M. A. from Yale. He was one of the founders of the Connecticut Medical Society.

[21] MSS. letter, Conn. State Med. Soc.

attend me at first, yet he thinks I may succeed." [22] Seven days later, John Trumbull writes to Walcott concerning it. "Dr. Hopkins has an itch of running away to New York, but I trust his indolence will prevent him. However if you should catch him in your city, I desire you to take him up and return him or secure him so that we may have him again, for which you shall have sixpence reward and all charges." Prospects must have brightened up considerably a little later, for on November 28, 1790, he writes: "I have been very busy." [23] About this time, he bought Captain William Bull's house and was able to finish his payments on it in three years. Here he lived, as I have previously mentioned, until his death, although in a letter to Barlow he showed he was somewhat dissatisfied with the location and thought he ought to live in the middle of the town, which was then in what is now the midst of the east side of Hartford.[24]

In accordance with the custom of that period, Hopkins received medical students for instruction. In one of his letters, in 1791, he states: "I still keep a roomful of pupils," [25] and one of these we know was Elisha North, afterwards an eminent practitioner of Goshen and New London, Connecticut.[26] Subsequently, in a letter to Barlow, he writes: "I still keep up my medical school, and have now five pupils—all promising young men—with me." [27]

Other letters speak of his inoculating patients against smallpox. In one from Litchfield we read: "I can inoculate Mr. Pumroys sones as soon as they choose, provided they will bring some fresh infection, for I have none but such as I have kept over the summer which is far from being as certain of taking effect as fresh matter. They may very safely bring it on a thread well corked in a small vial." [28] Later, when he had moved to Hartford, he writes, on August 21, 1793, that he was buried in inoculation of smallpox. "This business," he adds, "is much like that of the Treasury Department [29] in regard to exciting jealousies, raising party spirit, etc., yet from certain causes, my particular mode of conducting it, in case of any suspicion of wrong measures, does not admit of so unanswerable justification. When we first set up the business, in the spring, the disorder proved unusually churlish in all the hospitals in these parts; but as the summer advanced the patients had the disorder sufficiently light. We have only lost an infant of Mr. Colts between 3 and 4 months old, tho' we have inoculated upward of 200 patients. The Hospital kept me very busy for a long time; but 'tis now well established and gives me but little trouble. My own family have been inoculated among the rest and had the disorder favorably. It even cured Nancy of an illness which had been several months upon her." [30] In this year we learn Hopkins made free use of his new invented Calomel Pill. "Between 40 and 50 patients had gone through the eruption, more than half of which took it for the only mineral medium." . . . . "You may well judge," he adds, "I shall proceed with my *pill*." [31]

His great specialty, however, was tuberculosis and patients with this disease came to him for treatment from a great distance—one being recorded to have made the trip to Hartford all the way from New Orleans. Probably his success in this field was due to his close adherence to the advice he gave others, who would pursue this same line of practice. "But if any one aspires to gather laurels in this barren, ghostly field of practice he must be studious, critically observant of symptoms, inventive, copious in resources, persuasive with his patients and persevering in his endeavors. In this way I have no doubt but many may recover from an early stage of Phthisis. In some instances perhaps the emaciated hectic may return as it were from the tomb." [32] Indeed he believed so thoroughly in the idea that pulmonary tuberculosis was curable that we frequently find reference to it in his writings. For example, in one of his letters he states "such persons (*i. e.*, the tuberculous) may often recover though hectical if we perseveringly use proper means.[33] Unfortunately most physicians adopt the common opinion which by the way is carried much too far, that is, that the Hectick is at all events a mortal disease and hence are not apt to be very assiduous to effect what they take for granted is impossible." [34] He also appreciated the fact that proper treatment must be instituted early, and in one case declares it is very necessary that her parents be aware that a desultatory course is hazardous.[35] His treatment, too, was most judicious for those days, and did not consist, as we shall see, in the indiscriminate use of drugs. Amidst the polypharmacy of that period, it is refreshing to read: "Physicians are apt to treat this disorder with a dull formal round of inert or hurtful medicines."

His Treatise [36] on Consumption exists only in a manuscript copy, as the original manuscript has disappeared. It was in the possession, the copy states, of Dr. Mason F. Cogswell, an eminent surgeon in those days, but I have been unable to trace it. The copy is written in a very legible hand, but it was evidently transcribed by one who was inexperienced in medical terms. Consequently some of the errors are unable to be deciphered. It is to be found in the manuscript volume of the Transactions of the Hopkins Medical Society—a society established in Hartford County, in 1826, and named in honor of Dr. Lemuel Hopkins. In this treatise Hopkins discusses the purulent variety of consumption and

[22] Marble, op. cit., p. 143.
[23] MSS. letter, Conn. Hist. Soc.
[24] Todd, op. cit.
[25] MSS. letter, Conn. Hist. Soc.
[26] Dr. Elisha North, One of Connecticut's Most Eminent Medical Practitioners. J. H. H. Bull., XIX, 1908, p. 301.
[27] Todd, op. cit.
[28] MSS. letter, Conn. Hist. Soc.
[29] Letter to Oliver Walcott, then Auditor, U. S. Treasury.
[30] MSS. letter, Conn. Hist. Soc.
[31] MSS. letter, Conn. State Med. Soc.
[32] MSS. Treatise on Consumption.
[33] MSS. letter, Conn. State Med. Soc.
[34] MSS. Treatise on Consumption.
[35] MSS. letter, Conn. State Med. Soc.
[36] MSS. Treatise on Consumption.

states at the beginning the fact too few realize to-day: *"the earlier the treatment, the more likely the cure."* As to predisposing causes, he thinks apart from temperament and peculiarity of structure, it is found in the mode of life which induces local or general debility. It occurs in the races more frequently, who show a higher degree of civilization, but Dr. Rush was wrong when he said it was unknown among the Indians of North America. It is no respecter of persons as those extremely well built and healthy may succumb, although the substitution of the steel and nitre for balsams and syrups of bluopane (?) have lessened the number of deaths of such cases by curing them. He then details eight examples of Herculanean victims to tuberculosis, one of whom was his uncle, Jesse Hopkins. Debility is brought on by close rooms, tight dressing in infancy, want of proper nourishment, the excessive feeding of sugar to children and the neglect to frequently wash the skin of children with cold water. Imperfect respiration may predispose to a chest formation favorable to this disease. Most of the cases are seen between the sixteenth and thirty-sixth year. He thinks the theory that tubercles cause tuberculosis comes from a very dissecting age, yet has no doubt but that they are a frequent cause of hectics. He considers scrofula another cause, and smallpox and measles, especially of the exanthematous diseases, are remote causes of consumption. In discussing the onset of the disease, he refers to two different modes of attack: (1) with hæmoptysis, attended with cough and fever which gradually assumes the hectic form, and (2) with a cough and slight fever only, which advances with less alarm and more insidiously to the same unhappy state. Before discussing the symptoms in these two varieties of consumption, he makes the remarkable statement that blood spitting by relieving a congestion and local inflammation, in patients with chronical affections, is very apt to ward off phthisis. He continues "the chief difference between those, who spit blood and those who do not, may be that the former are more sanguine, irritable, slender and soft fleshed. Some difference too in the local affection may be easily conceived as more or less favorable to a præternatural motion in the lungs favoring an effusion into the bronchi."

Hæmoptysis, he says, is seen soon after taking cold, too hard exercise, the agitation of certain passions, the sudden increase of external heat and the use of vicious liquor, all of which are its immediate causes. It is mostly seen in the spring and fore part of summer. He considers it a spontaneous, natural effort to relieve congestion. Consequently physicians, friends and patients should not be alarmed by it, as we ought many times to expect benefit from such voiding of blood and expect that it will and ought to continue some time, at any rate till the congestion is removed. In the meantime it is best to keep the patient in a cool, quiet hopeful state, give cool drinks with perhaps nitre, the effervescing neutral mixtures or vegetable acids. If inflammatory fever, oppression and pain in the chest follow, enjoin rest, draw blood, blister the pained parts, keep the bowels open and use purges or 'glysters with cooling cement. The same kind of medicines should be continued *pro re nata* till the symptoms subside. If the patient does not recover, a hectic fever may ensue. Such a line of treatment Hopkins states, from fifteen years pretty extensive practice, was sufficient in all but two cases to restrain the loss of blood within due bounds. In these two cases the bleeding was accompanied, if not caused, by ulceration.

If the hæmoptysis is immoderate and apt to recur, astringents may be indicated. They should, however, be rarely used as their effects are uncertain and they are apt to be hurtful because they have the tendency to counteract syncope which is a very powerful means of stopping the flow of blood. Japan earth, cranes, billroot, Bristort (?) or pomegranate peel are among the best to employ. The best refrigerant is nitre, if taken in large doses, while it is dissolving. Hopkins had given as much as an ounce in twenty-four hours and thought it was best administered in thick barley water, some other mucilaginous drink or mixed with conserve of roses, being swallowed without dissolving and barley water or the like drunk upon it. However as its too long copious use is apt to disagree with the stomach, it is best to use it freely at first, and then let the neutral effervescing mixture and acids take its place. After the congestion is relieved, in some cases of plethora and sanguine temperament it may be best to let blood freely while the patient is in an erect posture so as to produce syncope.

If hæmoptysis be moderate yet continues to resist the above means, as well as blisters to the chest, it may be proper to give a vomit of ipecac and repeat if necessary. He generally gives five grains of ipecac for this purpose and repeats the dose every half hour until it is effectual.

The second mode of attack is seen in those not so sanguine, slender or diaphanous. It begins with a small and commonly a dry cough and some fever, together with some pain about the chest, shoulders and scapula. The approach is generally so insidious that the hectic or second stage appears before the alarm is given. If the symptoms are considerably inflammatory, it is better to oppose them assiduously till they give way by bleeding, cooling laxatives, blistering the chest, refrigerants, dilution and low diet. We must support the patient, at least not weaken him unnecessarily, enjoin proper exercise in the open air, acid and sub-acid fruits, milk and vegetable diet. The patient should sleep in well-aired rooms and on hard beds, should wear flannel next the skin and have external friction applied. These means are more congenial to our natures than medicines strictly so-called and therefore more grateful to patients and hence may be used copiously and for as long a time as can ever be necessary. On the whole, while exercise, flannel and friction support an equal distribution of the circulating fluids, air, acid fruits and diet sufficiently mild are refrigerant enough for such cases generally.

If inflammation and congestion be absent or slight, he recommends small pukes, as they are the most powerful means we have of promoting all the secretions. They are considerable evacuants. They not only evacuate from the stomach

and biliary vessels, but are efficacious, perspiratives, sudorifics and expectorants. They powerfully excite the circulation in the superfices of the body and are therefore well adapted to relieve moderate degrees, at least, of pulmonary congestion and inflammation. They may be given daily for a while, in some cases, or at less frequent intervals. It is best to use them at first pretty assiduously and then let them give place to the general treatment of exercise and diet, to be detailed later. The best clue we can follow as to their use is furnished by the effects of the first doses. Hopkins has generally found hectics an easy class of patients to puke. The exercise which is proper for such patients should be sufficiently constant, gentle at first and capable of being increased as the patient will bear. It must be persisted in. The diet must be mild but generous. The bark may be used, but the steel is too heating for such patients. The cold bath may also be well employed but should be cautiously used for those hectically inclined. It is a peculiar remedy in weakness, it abates irritability, warms the superfices and hardens against colds from slight accidents, in a most remarkable manner. The cleanliness and refreshment it occasions, when frequently used, are also much in its favor.

The first stage of athletic hectics is peri-pneumony but it is not as acute as the more common form. These cases used to be called quick consumption. Though Hopkins has had little experience with them, yet he judges they can always be cured by peri-pneumonick treatment, if continued longer than in the common acute cases. These patients require antimonial pukes. A thin cooling diet is necessary and acid fruits, with perhaps neutrals, liberally. Large blisters should be applied to the painful parts and when the ulcer is almost healed a large drain from an issue, to prevent a new inflammation from coming on.

In the hectic stage, Hopkins thinks pukes are the best substitute for exercise, as they relieve the lungs of a pituitous and purulent load. He gives the practice of Dr. Reid and Dr. Mariat in this respect and thinks any medicine is a poor substitute for exercise. Bleeding is generally contra-indicated as it would reduce the patient unnecessarily. Hopkins administers nitre to these patients by mixing one drachm of it in half a pint of water and adding a large spoonful of genuine rum, and loaf sugar to the person's taste. The nitre is stirred into this mixture just before it is drunk and has proved very refrigerating. He has given several pounds of nitre, in this way, to such patients. The diet must be most generous, carefully prepared and varied to their varying taste, together with strong bitter beer, genuine cider or generous wine. Lean savory broths, plump lean flesh, eggs and shell fish are particularly proper. The lean of good beef roasted rare with plenty of the red gravy seemed to Hopkins very advisable. Bitters are often useful and the bark sometimes though Dr. Fothergill disapproved of it. If we have not been successful in warding off a tuberculous suppuration from patients in the inflammatory stage we should trust wholly to a course of habitual exercise.

In the hectic stage the following are useful: a few pukes, some neutral effervescing draughts, blisters to the painful parts and the use of summer and fall fruits. One must be attentive to find out what diet suits them best and their confidence must be won so that whatever we point out for them to execute, they will cheerfully and perseveringly prosecute. When this is done, we should rely solely on sailing, riding or in certain cases of poverty, etc., on some other kind of exercise, without being very particular as to diet, accommodations or weather. In regard to those who cannot, will not or dare not go abroad we should be inventive in pointing them out proper exercises about home so as to prevent a tiresome or even an unamusive round of them. Some may ride as posts, others as pedlers, some may take short journeys to see their acquaintances for considerable time. Those who have no business may vary their routes in all directions. "I am persuaded," he continues "there are many employments of labor which the poor may follow very constantly rather than commence (to be) mere spectators of their own decline." A swing may be of much advantage to some; this exercise certainly makes the pulse slower. It also helps to cool the body in hot weather. Besides it is the most gentle of all exercises and however otherwise confined they can use this on a swinging bed. Even those who ride about home or perform other exercises can, if they please, use this every moment both night and day while in the house for swinging may be effected in a mechanical way. Hectics soon become hot and febrile if they lie down on a feather bed, as it promotes sweating. Consequently hard beds of straw are preferable. The patients should cover themselves as lightly as they can, with comfort. Their sleeping rooms, in hot weather, cannot be too airy. Every window should be up and every door open provided a concentrated stream of air does not come directly on them. In all the hottest days of summer they should exercise very early in the morning and towards evening. During the hottest part of the day they should keep themselves as cool and quiet as possible, perhaps on a swing bed.

In any stage of treatment, except the last and for a short time during hæmoptysis, the patient should be given some exercise and this exercise must be increased as their strength will bear, until it takes the place of every other means. The weakest can enjoy swinging, those, who cannot ride on a horse, can yet ride in a carriage and the latter frequently soon prepares for the former. In some cases 'tis very necessary to provide a very easy going horse. The patients should always be instructed to ride or use other exercise in such manner as not to excite pain in the breast or increase cough. They should begin with morning rides when fever is longest (absent) and stop before the mid day rise. Those who commence journeying in the fall should travel southward. They should set off when such a temperature prevails as is most comfortable for them. For in this way they keep in such temperature the whole season. When they begin to journey in the advance of hot weather, they should rather travel a northern course till the heat abates. Whatever course they steer, they should not stop in a flat, unhealthy country but on

a hilly, healthy one. At the end of their outward course, they should not become remiss in regard to exercise of some kind or other, but should explore the country in all directions, hunt, go a fishing or join with those they fall among in their diversions, even on their journey. I think it would be a useful variety to walk considerably. It is to be remembered that patients require different degrees of exercise. Three or four thousand miles riding suffices for some, while others should enter upon it as a business for years and others again for life. Sailing has been recommended by some and has been said to have a great advantage by its constancy, night and day. In fact some prefer it on account of its gentleness, on the supposition that weak ulcerated lungs are apt to be hurt by the agitation of riding. Hopkins, on the other hand, thinks a certain degree of agitation is advantageous as it prevents congestion, in the lungs, from circulating fluids and frees the lungs of a purulent and pituitous load. Besides, if sailing were beneficial, he thinks England would have reaped benefits from this, as it is a land about equally of seamen and consumptives. Notwithstanding this, sailing may be useful in warding off the hectic stage. It may also be efficacious in an early stage of phthisis by exciting considerable vomiting, especially if the voyages be long ones.

The last stage is attended with ghostly emaciation, profuse nocturnal sweats, fascies Hippocratica, cough and diarrhœa. The only support of sinking nature is generous aliment and the only effectual palliative of cough, restlessness, depressing apprehension, pain and purging is opium. The patient should have the full benefit of it, even if the dose has to be increased.

Prophylaxis. The methods of preventing consumption will be the more efficacious the more early they are entered on. What has been called hereditary taint or predisposition does not, in my judgment, render phthisis a necessary event. I hope things are in a train to have communities of people act with the foresight and judgment of the more sagacious individuals of past ages. Children, born of weakly mothers and especially hectical ones, should have healthy nurses provided for them or be fed in the most judicious manner. They should be washed in cold water daily for several weeks after their birth. Then they should be plunged in cold water till they are about a year old. Through the stages of childhood and youth, they should also wash or bathe as often as they change their linen. This method, together with a plain diet, temperance in all things and some active employment in the open air, I conceive to be the best security against consumption.

The treatment, thus outlined in his treatise, is reiterated in five of his letters to his brother-in-law, Dr. Daniel Sheldon, a well known practitioner of Litchfield. In one of them he speaks of his fears that the patient is hectical but doubts the use of the steel, although possibly small bleedings might be advantageous on account of the patient's youth, the advance of spring, together perhaps with pain in the chest especially on coughing. If bleeding should be done it should be accompanied by the blistering of the pained parts of the chest and the administration during the exacerbations of fever of neutral effervescing mixtures. Whatever course be pursued, he adds, riding on horseback will either now or when the lancet, etc., shall cease to be useful, prove paramount to every other course.[37] After he wrote this, he saw the patient in the mid-day exacerbation of fever and advised two or three bleedings in the arm for 'tis often on the 3d or 4th bleedings that the pains in the chest subside. In his judgment what can be done apart from riding will pretty soon be known and the above treatment will only prepare for riding.[38] In another letter possibly referring to the same patient he doubts the use of bark and steel from the appearance of the top of her head, the (?) form of her nails, parch'd lips, dry cough, increased on lying down, chills, etc. He acknowledges the difficulty in determining in these cases whether a mode of practice suited to hectic or chlorosis should be pursued. If there is as much of the hectic or at least of tendency to it, he declares it might be well to use only a bitter of Columbo cum Cinnamon and Cort. Aurant. for flavor, along with less Tinct. Thebain to palliate cough and procure rest at night. For the rest, to trust to diet and exercise.[39] A third letter details the course of treatment he pursued in looking after a man with tuberculosis, whom he appears to have sent to Litchfield to be under Dr. Sheldon's care. In this case, neutral mixtures, diet, bleeding for the pain in the chest and exercise were prescribed. He adds: I am much interested in his cure. He is a very good man—is very anxious to get well—very generous and willing to pay and mind his doctor.[40] Still another letter to his brother-in-law gives the findings at the autopsy, in one of the Herculanean victims to tuberculosis whom he refers to in his treatise. The patient was six feet in stature and rather corpulent, every way well formed. He was attentive and ingenuous in regard to the means of preserving health. He was a farmer as well as a clergyman and therefore used considerable exercise. He was not in any respect intemperate nor do I know tho' almost weekly at his house that he was in any mistaken habit of living. His last illness commenced in 48th year of his age and continued 18 months. But his disease tho' a pulmonary consumption was not of the purulent kind. It began with a pain in his side between the os illium and short ribs which increased gradually, lancinating pains came by degrees, to be propagated in various directions. He had, when the disease was fully formed, frequent sensations as tho' a curry comb, as he said, raking him from the part first affected across the bottom of his belly—the same sensation was also frequently extended upwards and across his breast. He was attended early with a slight fever and small cough, both of which very gradually increased. The fever rose but once a day. He expectorated only pellucid mucus, which by degrees became more and more tough and even gelatinous, for it would roll on the floor when

[37] MSS. letter, Conn. State Med. Soc.

[38] MSS. letter, Conn. State Med. Soc.

[39] MSS. letter, Conn. State Med. Soc.

[40] MSS. letter, Conn. State Med. Soc.

a little dusty like a jelly. He had but little stimulus to cough; but as he expressed it, coughed from judgment when he felt the phlegm move in the lungs. He died as much emaciated as common hectics—and like them had thrush in the last stage. His feet and legs did not swell.[41]

In the autopsy the following things were remarkable: 1st, The left lobe of the lungs had shrunk up to the size of a goose egg, appearing tuberculous and adhering on the back part of the pleura. 2d, The left cavity of the chest contained about five pints of water and there was some in the abdomen. 3d, The 6th and 7th of the true ribs counting upward had nodes or exostoses on them, where they were connected to their cartilages, of the size of a chestnut. These ribs were more brittle than the rest; tho' I think several more of the ribs on that side, perhaps all of them, were more so than common. 4th, The external flesh of that side was compact and knotty, containing also a number of bones from the size of a pea to that of a nutmeg. These were contained in such kind of flesh as appeared in bunches all about that side. The bones were of various figures and hardest in their center. They were not only external but internal also—about half a dozen of them were found adhering to the peritoneum, close by the back bone, just under the diaphragm. One was found in the cavity of the chest. Five or six were clustered together in the external flesh, at the spot where the chief seat of his pain always had been (in his treatise he says this disorder was probably occasioned by his having, a few months before on the same side, the herpes exedens, vulgularly called shingles, for the effects of the herpes seemed as it were to spin out into his last illness). Liver, gall-bladder and other viscera sound. I forgot to tell you that the intestines adhered fast to the left side.[42]

Oliver Walcott's sister's illness occasioned a number of letters to pass between Walcott and Hopkins. She seemed to have found his treatment rather vigorous and rightly, as from her description, it may properly be called heroic: "I am laid every night upon a bed of straw, and even this will not long be allowed me. In the morning I am plunged in cold water, or rather have it poured upon me, till my breath forsakes me, and then they take the hint and wrap me in a warm blanket till they perceive life returning. I am then compelled to swallow nauseous drugs to sharpen my appetite for a dish of soup meagre, which is my breakfast." [43] Nevertheless she improved under this treatment, for Hopkins writes on December 2, 1789, Mrs. Goodrich is much better. Her fever, cough, etc., have for several days almost wholly subsided.[44] Seven months later he says: "I have perseveringly insisted on her riding very early in the morning and again at evening, daily. This, together with her two last journeys which repress'd her worst symptoms, have so far mended her health that I am almost certain 'tis yet possible for her to regain it entirely." [45] This seems to have been the case, for on April, 1791, we learn: "Her general health seems to me to be pretty well restored and I cannot see particular dangers of relapse. The local disease in her wrists too I believe is cured. By careful attention to the tumour I found there were some concretions in it of pretty firm texture. This symptom is said by Doct'r Bell to denote that the tumour originated from a spasm and that laying it open with the knife is the proper mode of cure. As I had no experience in such cases I confided wholly in Bell's account of the matter, and declared for the operation. Doct'r Cogswell performed it. As soon as the opening was made a number of concretions, mentioned above, rushed out in quick succession; these amounted to 25 in number and were, at an average, about the size of a pea. They were of a roundish form and appeared like so many pieces of beef sinue. They were compressable between the fingers like calk wood; but were much too firm to be broken by such compression. The sore is nearly healed and I have very little doubt but that the cure will become complete." Such however does not appear to have been the case, as two years later he writes: "Dr. Cogswell put a seton into that troublesome tumour on Mrs. Goodrich's wrist about two weeks ago. The pain and inflammation ran too high and made us fear danger; but these are now repressed in due degree, and we hope for a radical cure." [46]

During Hopkins' time, the other great authority, in this country on tuberculosis was Benjamin Rush, of Philadelphia. Whether these two eminent phthisio-therapeutists ever met is doubtful, but certain it is that Hopkins wished to become acquainted. In April, 1791, he writes the following, to Oliver Walcott, who had just gone to Philadelphia as auditor of the United States Treasury: "Have you met Dr. Rush? If I ever go to Philadelphia, I shall want especially to become acquainted with him as being of my profession, and I hope to be introduced to him by you." [47] Elsewhere we read in another letter: "Doct'r Rush lately wrote me that he still cures hectics by first reducing the pain in the chest by ye lancet—then by tonics, especially riding," [48] so we know they were correspondents on the treatment of tuberculosis. Their treatment also was very similar, as the following letter of Rush will show, which we shall place by the side of one from Hopkins. The former is the more explicit, as it was written to a patient, while Hopkins' letter was designed for a physician. What I have already written of Hopkins' treatment should also be here considered:

[41] MSS. letter, Conn. State Med. Soc.

[42] MSS. letter, Conn. State Med. Soc., and MSS. Treatise on Consumption.

[43] Memorial of Henry Walcott, New York, 1881, p. 321.

[44] MSS. letter, Conn. Hist. Soc.

[45] MSS. letter, Conn. Hist. Soc.

[46] MSS. letter, Conn. Hist. Soc. Mrs. Goodrich died in 1805.

[47] MSS. letter, Conn. Hist. Soc.

[48] MSS. letter, Conn. State Med. Soc.

Dr. Rush's Letter.

Sir.—The following remedies appear to me to be proper in your case:

1. A powder composed of the Rust of Iron in fine powder two ounces, ginger in powder an ounce, Columbo root two drams, intimately mixed together. Of this a *small* teaspoonful should be taken every morning and evening in a little syrup of molasses.

2. A diet consisting chiefly of the lean of fresh meats, particularly beef, mutton and wild animals, salted meats, fish, toasted bread, or the crust of bread, or biscuit not toasted, with potatoes. Strong tea and coffee should not be tasted. Very weak coffee or tea may be taken in the mornings and evenings with a little animal food, or bread and cheese. Chocolate or gruel or Rye or Indian mush with molasses and butter, or with unskimmed milk, may be taken in the mornings and evenings instead of weak tea or coffee, or the other articles mentioned to be taken with them. *Old* white wine of any kind, or porter, or ale may be taken in small quantities diluted, or alone with your mid-day meal. Toast tea may be taken between your meals when you are thirsty. Small and frequent meals should be preferred to but two or three in a day, so as to prevent your ever feeling the inconvenience of a full or empty stomach.

3. Use constant but gentle exercise for some months to come but never before breakfast or soon after eating nor after sun down, nor in very hot or cold weather, nor to such a degree as to bring on fatigue. A long journey should be preferred to short excursions from home in order to derive the greatest advantages from exercise.

4. Change your dress with the weather, preferring always clothing that is rather warmer than agreeable to health.

5. Go to bed early and avoid sleeping constantly on one side.

6. Obviate costiveness by chewing or swallowing occasionally a little of the root of Rhubarb.

7. Should you be affected with a return of the disease in your breast, and it should be attended with a *full* or tense pulse, lose a few ounces of blood, and apply a blister to your breast. If the disease in your breast be light and not attended with a *full* or tense pulse a blister along will probably relieve it.

8. Should you be affected at any time with great pain in your breast or stomach, or back or bowels without fever or with a lax. take 10 or 15 drops of laudanum every hour until you are relieved.

9. Continue the disuse of tobacco.

10. The Warm Bath will be useful when you are much fatigued or feel more pain in your limbs or depression in your spirits than usual.

11. On the days that you do not exercise out of doors let a servant rub your body for ten or fifteen minutes with a flesh brush, or a piece of coarse linnen or flanel.[50]

BENJN. RUSH.

July 19, 1812.

Dr. Hopkins' Letter.

Am of the opinion that the things principally to be depended on are riding on horseback, sailing, friction, a diet primarily of milk with roast apples, etc., together with the greatest variety that can be obtained of acid, sub-acid saponaceous fruits used in any form best relished—whey made by boiling milk with sub-acid saponaceous fruits and sweetened to her taste with honey or loaf sugar—barley water and viper's flesh. Among the fruit kind am particularly fond of apples, tamarinds, pine apples, oranges, lemons, currant jelly. Also issues and a plaster of Pitch with one 3d or 4th bees-wax melted with it, applied to the back. Were I to advise anything more than the above well timed and thoroughly persisted in should chuse lac-ammonia or a solution of gum asafoetida and ammonia to be taken before her coughing turns in ye morning. The foliated tartar with opening roots or the Mist, Anti-emet, or a neutral mixture in whey at other times withal. Perhaps a large blister on her side or back may be of service.[49]

Hopkins' Treatise[51] on Common Cold or Catarrh is an ingenious essay to prove that heat is the immediate cause of colds. This conclusion was the result of investigations he had carried on, being led to it by his tuberculous family history and his tuberculous build. For next to diet and exercise he found the avoiding of frequent colds was to be strictly and habitually attended to. He also soon found the common theories as to the origin of colds were unreasonable, and observation gradually taught him that colds were most apt to come on in the fall, winter and spring, whenever the weather became suddenly warm. A constant habit of attending to the first symptoms of colds in himself proved that they made their first approach in a close room, kept hot by a fire, particularly the rooms in brick houses, and especially when such rooms were crowded with people. On mentioning his theory to some friends, it did not meet with their unqualified approval and other causes were given. Some, however, confirmed his observation, and Tapping Reeve told him that Doctor Franklin in his treatise on the use of stoves had intimated an opinion to this effect, *i. e.*, that people were more apt to take cold by staying in rooms heated by stoves than by passing from them into the open air, and that the doctor represented that he had received this hint from a German physician, who lived where stoves were much in use. Finally he thus sums up his doctrine: Exposure to cold,

[49] MSS. letter, Conn. State Med. Soc.

[50] MSS. letter in possession of Dr. Henry M. Hurd, to whom I am indebted for his kindness in allowing me publish it.

[51] MSS. Treatise on Common Cold or Catarrh.

being a removing of the stimulus of heat, prepares the body and especially the passages of the breath, the eyes and cavities of the ears to a higher operation of heat in proportion to the term and degree of such exposure, that dampness aids and debility favors the same operation of cold—that on passing from cold air, into warm rooms, the heated air stimulates the mucous membrane of the passages of the breath, etc., that this stimulus excites too rapid a motion in the vessels of those parts in different degrees, according as these causes have operated more or less powerfully; that this mere action is always of an inflammatory nature and may exist in any degree from a slight cold to a severe peri-pneumony, that therefore cold is the more remote and too warm air the more immediate cause of colds, that cold air instead of being the immediate cause is in fact the best adapted cure that can be applied.[52]

Besides his skill in treating tuberculosis, he also excelled in the treatment of chronic diseases and intemperance. He was noted for his cooling treatment of fevers, especially puerperal, and his use of wine in typhoid, advocating the antiphlogistic regimen and practice as opposed to the alexipharmic.

But few of his poems can now be distinguished. Those that are known are chiefly remarkable for their sharp, bitter biting wit, expressed in their assaults against charlatanism, hypocrisy and infidelism. They also glow at times with patriotism and love of country, as well as with their advocacy of Washington and Federalistic principles. His poem on the Cancer Quack is a satire on those charlatans who claim to be able to cure cancer by secret remedies. It is said, according to his pupil, Elisha North,[53] to have had the very excellent effect of driving a noted cancer quack from Hartford. It begins thus:

Here lies a fool flat on his back,
The victim of a Cancer Quack;
Who lost his money and his life
By plaister, caustic, and by knife.

It then states that a pimple rose, southeast a little of his nose, and daily grew bigger by too much drink. Finally, after a score of gossips had recommended different modes of cure without benefit, he sees a handbill in the weekly news:

Signed by six fools of diff'rent sorts,
All cur'd of cancers made of warts.

Winged by fears, he goes in quest of this cancer-monger, but on his way finds another, who tells him this pimple's name is cancer and adds:

I've sweated hundreds out with ease
With roots as long as maple trees;
And never failed in all my trials—
Behold these samples here in vials!

[52] His only medical contribution in print is a "Case of Biliary Calculi" in Communications of the Medical Society of Connecticut, New Haven, 1810, I, pp. 75-78. It details the history of a woman, aged 52, who had had several attacks of jaundice. Finally in one attack she passed two gall-stones, the size of a hazel-nut and a walnut, and all her symptoms immediately subsided.

[53] North, Outlines of the Science of Life, New York, 1829, p. 113.

The bargain is consequently struck, but the plaister gnawed his face without effecting a cure. Finally the doctor, foiled, swore it was a right rose cancer sore and probed it. He then continued his heroic treatment until one broadside of the patient's face was devoured.

Courage 'tis done, the doctor cried,
And quick the incision knife applied
That with three cuts made such a hole,
Out flew the patient's tortured soul!

The moral runs:

Go readers, gentle, eke and simple
If you have wart or corn, or pimple,
To quack infallible apply
Here's room enough for you to lie.
His skill triumphant still prevails,
For death's a cure that never fails.[54]

The Hypocrite's Hope was, if anything, even more ironical. It describes a man who early betook himself to saintship and confessed in church how he became converted. It continues:

He stands in half way covnant sure
  Full five long years or more
One foot in church's pale secure
  The other out of door.

Then riper grown in gifts and grace
  With ev'ry rite complies
And deeper lengthens down his face,
  And higher rolls his eyes.

He tones like Pharisee sublime
  Two lengthy prayers a day,
The same that he from early prime
  Had heard his father say.

His close attention in church is then related and how he arises when the priest appeals to the old ones born anew:

Good works he careth nought about,
  But *faith* alone will seek
While Sundays pieties blot out
  The knaveries of the week.

He makes the poor his daily pray'r
  Yet drives them from his board
And though to his own good he swear
  Thro' habit breaks his word.

This man advancing fresh and fair
  Shall all his race complete;
And wave at last his hoary hair
  Arrived in Deacons Seat.

There shall he all church honors have
  By joyous brethern given—
Till priest in fun'ral sermon grave,
  Shall send him straight to heaven.[55]

Equally severe and sarcastic was his poem on General Ethan Allen who had just published something derogatory against the Bible:

[54] American Poems, Litchfield, 1793, p. 137. This collection was edited by the talented Dr. Elihu H. Smith, of Litchfield, and later of New York.

[55] Ibid, p. 139.

Lo Allen 'scaped from British jails
His tushes broke by biting nails.
Appears in hyperborean skies,
To tell the world the bible lies.

* * * * * * *
* * * * * * *

Behold inspired from Vermont dens,
The seer of Anti-Christ descends
To feed new mobs with hell-born manna,
In Gentile lands of Susquehanna;
And teach the Pennsylvania Quaker
High blasphemies against his Maker.
Behold him move ye staunch divines!
His tall head bustling through the pines;
All front he seems like wall of brass,
And brays tremendous as an ass;
One hand is clenched to batter noses,
While t'other scrawls 'gainst Paul and Moses.[56]

He was also the author of New Year's Verses for 1795 and the Guillotina,[57] both of which dealt largely with the political topics of those times, in which Hopkins was deeply interested. They were published in the Connecticut *Courant*. His writing in conjunction with the other Hartford Wits consists of three productions: The Anarchiad,[58] The Echo and The Political Green House.[59] The Anarchiad was written with Trumbull, Humphreys and Barlow and was a political satire designed to show how futile a government of states was without a strong bond of union between them, effected by delegating certain powers to a central government. It appeared in several numbers of the Connecticut Magazine, during the Confederation, in 1786-1787, when there was no strong tie between the states and no regard for the general welfare of the country. This naturally led to great disorders and it was to the promoters of these disorders that the poem was addressed. It was supposed to have been found in digging among the ancient aboriginal fortifications in the western country, and, by the aid of vision and prophecy, it was made to bear on modern events. The plan of the work was suggested by Humphreys from his acquaintance with an anonymous English satire, the Rolliad. It was designed to arouse public curiosity and teach lessons in patriotism. How many of the American antiquities or numbers (there were twelve in all) of this poem Hopkins had a hand in, we do not know. He is supposed to have been the sole author of the tenth which, as the speech of Hesper, makes a strong appeal for a centralized government, especially in its concluding lines:

But know, ye favor'd race, one potent head
Must rule your States, and strike your foes with dread
The finance regulate, the trade control
Live through the empire, and accord the whole.

[56] Ibid, p. 142.

[57] The Echo, with other poems, 1807.

[58] The Anarchiad, New Haven, 1861. This volume was edited by Luther G. Riggs.

[59] The Political Green House was published with the Echo, op. cit.

Ere death invades, and night's deep curtain falls
Through ruined realms the voice of Union calls;
Loud as the trump of heaven through darkness roars,
When gyral gusts entomb Carribbean towers—
When nature trembles, through the deeps convuls'd,
And ocean foams, from craggy cliffs repuls'd;
On you she calls! attend the warning cry:
"Ye Live United or Divided Die!"[60]

The Echo was a medley of burlesque and satirical pieces, which may be called a continuation of "The Anarchiad." They were written by Alsop, Theodore Dwight and Hopkins, as Barlow and Humphreys were abroad and Trumbull took no part in their production, although he evinced a striking interest in them. The first number appeared in *The American Mercury*, a Hartford newspaper, in August, 1791, and was written by Alsop and Theodore Dwight, at Middletown, with the object of amusing themselves and a few personal friends, by ridiculing an inflated description of a thunder storm. It was not intended for publication. From ridiculing the mode of writing in those days, the authors passed on to the consideration of politics and proved themselves to be strong supporters of Washington and the Federalists. The numbers of the Echo were finally collected and published in book form, though not complete, in 1807.[61]

Unfortunately we do not know the number of which Hopkins was the joint author. He is supposed to have written entire the eighteenth Echo which was separately published in 1795, entitled "The Democratiad." It had for its object the ridiculing of Democrats and Jacobins, including Senator Mason, who sent for publication a copy of Jay's treaty to Mr. B. F. Bache, Franklin's grandson. Bache was editor of the *Aurora* and to him the poem was addressed.

Thou great descendant of that wonderous man,
Whose genius wild through all creation ran—
That man who walk'd the world of science o'er,
From ink and types to where the thunders roar,
To thee friend Bache, these lines I now address,
Prepared on purpose for thy hallowed press,
I've picked thee out because I highly prize,
Thy grandsire's memory and thy knack at lies.[62]

The Political Green House, written also by Alsop, Theodore Dwight and Hopkins, was patterned after the new year's verses of that period and is almost entirely devoted to a consideration of politics. The following reference in it to yellow fever is supposed to have been written by Hopkins:

Learn then Columbians, ere too late,
If not to cure, to ward the fate;
For when swart skies find filth beneath,
They breed swift messengers of death.
Let Belgian neatness mantle o'er
The marts and towns around your shore;
And ere the Dog Star's sultry rays
Dawn and decline with solar blaze,
Stretch daily in warm baths your limbs,

[60] Op. cit.

[61] Op. cit.

[62] Op. cit., p. 128. The last two lines were omitted when the Echo was published in book form.

Or lave you o'er in tepid streams.
Let no late revels break your rest,
Nor passion rankle in the breast;
The strictest temperance of the board,
And glass, can potent aid afford.
From ardent spirits must refrain
Dire source of disease and pain
Ye heirs of wealth! to rural seats
Retire from summer's scorching heats,
And let the virtuous sons of want,
Throng gladd'ning round the sylvan haunt,
On tented plains; and often taste
With you the simple plain repast.[63]

Large features, bright staring eyes and long ungainly limbs, which gave him an uncouth figure, were combined with marked eccentricities of his character and very brusque manners, yet with them all he won the confidence and friendship of his patients to a remarkable degree. "His peculiar faculty," his nephew states "was intuitive and almost instantaneous perception of truth. The whole cast of his mind, and therefore of his conversation, was in the highest degree bold, strong, original, and his thoughts were very often uttered in nervous and concise figures of speech, entirely peculiar to himself and full of instruction and light. He was, in many respects, the most extraordinary man I ever knew, yet he has left nothing behind which will at all do him justice. He will live a little longer in the love and admiration of the good and wise of his acquaintance, who survive him, and then the memory will be lost to all human view." [64]

We also read his powers of abstraction were great and sometimes his interest in a subject would cause him to sit up all night, engaged in its study and oblivious to everything else. His constant devotion to his patients is likewise commented on. Occasionally he would deny himself all other calls to spend his whole time with a patient, even administering every dose of medicine himself. His memory is said to have been so retentive, he could quote any medical or literary article he had read, with the same readiness that a clergyman quotes the Bible. In his literary and scientific labors he was indefatigable, and was not only well read in the literature of his profession but also in that of the arts and sciences and modern literature generally. Pope and Milton were his favorite authors.[65]

Many stories are still extant about his peculiarities. It is related that the father of one of his patients, thinking there was little hope left, said to Hopkins: "My daughter is dying, had I not better send for a clergyman?" "No," replied Hopkins, "but you may send for the undertaker and have her measured for her coffin." Upon the rightly indignant father remonstrating, he explained, "My meaning is, you may as well send for one as the other; if your daughter is left undisturbed, and allowed to be quiet, she will recover, or I will forfeit my reputation: but if you disturb her as you propose, she will in my opinion certainly die." This advice the father followed and his daughter recovered.

After worrying about a patient, who was passing through a very critical period, he once passed a few sleepless hours at night, then got up, drove four miles to the patient's house and without speaking examined him to make sure the medicines did not require any deviation. Being thus assured that the patient was better, he left the house without having spoken to either the patient or the nurse.

On another occasion Hopkins entered a room where a sick child lay. The windows were all securely fastened, the curtains were closely drawn and the door was tightly closed after his entrance. Without at first noticing the child, he proceeded to roll up the curtains, raise the windows and open the door, to the amazement and horror of the child's parents. After Hopkins had carefully examined the child, he turned to its parents and said, "all that your child now requires is a little more of God's sunshine. Take it in your arms around the block daily and have plenty of fresh air in this room and recovery will soon follow." Subsequent events proved the wisdom of his advice. A somewhat similar story is told about his seeing a child ill with scarlet fever, under like circumstances. Without uttering a word, he took the child under his arms and brought it out of the house, placing it under a refreshing shade. The whole household and neighborhood followed, and threatened the doctor with broomsticks. He kept them off, however, and ordered wine to be brought and soon the child recovered.

Once he was called to see a woman, who had been subject to bleeding from the lungs, which had been stopped with great difficulty but she continued very ill. When Hopkins was called, he first endeavored to set the lungs bleeding again, to relieve the lungs congestion. This he is said to have done with perfect success, as it resulted in the patient's recovery.

One night when sleeping soundly from exhaustion he was called to see a man with supposed colic, as the man's friends were not satisfied with the prior treatment. After an examination Hopkins said: "He has not got the colic but a repellant and wandering rheumatism and treatment for the colic would have killed him." In this case also we read the patient recovered under Hopkins' treatment.

At one time he was called to see a case of gout, which only presented some cardiac complication. He was momentarily at a loss how to proceed. Finally he employed stimulants and when the pain in the big toe came on, he joyfully proclaimed: "Now I know how to treat you."

When the fever powders of a certain quack near Hartford were widely used, Hopkins is said to have seen with Dr. Cogswell a young woman, who was rapidly declining from pulmonary tuberculosis. A sister-in-law of the patient, believing in the efficiency of these powders, hesitatingly asked Hopkins if the fever powders would not be of service to the

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[63] Op. cit., p. 245.

[64] MSS. memoir of him by his nephew Samuel Miles Hopkins. I am indebted to the late Dr. George G. Hopkins, of Brooklyn, for his kindness in allowing me to examine this memoir. Later Miss Katherine Prichard, of Waterbury, had a copy made for me, from the one in her possession.

[65] See also the memoirs of him in Bronson's History of Waterbury, Waterbury, 1858, pp. 414-416; Anderson's History of Waterbury, New Haven, 1896, III, pp. 927-928; Thacher, op. cit.

patient? Much to her surprise he turned and blandly inquired if she had any of them. To this she assented and produced a dozen of the powders. "How are they to be administered?" asked the Doctor. "In molasses." This was brought, on his request, and he began at once to pour the whole contents of one of the papers into it. "Why, Doctor," the affrightened woman gasped, "the half of one of those papers will be a great portion for my sister." Not noticing this interruption, he calmly mixed in all of the powders and swallowed them, remarking to his friend Cogswell, "I am going to Coventry to-day. If I die from this you must write on my tombstone: 'Here lies Hopkins killed by Grimes.'"[66]

On March 24, 1801, we learn from his brother-in-law that he was very sick indeed with his cough, pain in the side and breast, attended with fever. The attack had come on him in Waterbury, where he was bled and blistered. He with difficulty got home and had been confined to his house ever since. Later "he was bled repeatedly, notwithstanding the opposition and remonstrance of his medical friends, lived upon the lowest diet, and took repeated doses of neutral salts," yet lived to resume somewhat his practice.[67]

One day he was brought back from a patient's house with his legs swelled to his knees, with an entirely inelastic feel, great oppression of breathing, depression of strength, much altered countenance. "He appeared to be dying," Sheldon, his brother-in-law writes,[68] "and his last conversation has been calm, religious and like a good man." Shortly thereafter he paid the great debt of nature, on April 14, 1801. At his death he stood at the head of the medical profession in Connecticut.[69]

"Such was Dr. Hopkins; his life was full of incidents, full of usefulness, full of honor; he lived, the admiration of his friends, he died, deeply and extensively lamented with the blessings of thousands resting upon him."[70]

[66] Everest, The Poets of Connecticut, New York, 1847, p. 52.

[67] MSS. letter, Conn. State Med. Soc.

[68] Thacher, op. cit., p. 301.

[69] MSS. letter, Conn. State Med. Soc.

[70] Thacher, op. cit., p. 304.

NOTES AND NEWS.

Dr. Joseph Akerman is Superintendent of Health for the City of Wilmington, N. C. Address: 311 North Front Street.

Dr. Herbert W. Allen is Instructor in Clinical Pathology in the University of California. Address: 240 Stockton Street, San Francisco, Cal.

Dr. George Blumer is the John Slade Ely Professor of the Theory and Practice of Medicine, Department of Medicine, Yale University.

Dr. Camillus Bush's address is 126 Stockton Street, San Francisco, Cal.

Dr. Joel I. Butler is Instructor in Surgery, Yale University. His address is 192 York Street, New Haven, Conn.

Dr. W. J. Calvert is Professor of Medicine, Baylor Medical School, Dallas, Texas. Address: 322 Luiz Building.

Dr. C. N. B. Camac is Professor of Clinical Medicine, Cornell University Medical College and Visiting Physician to the New York City Hospital.

Dr. Benson A. Cohoe is Professor of Anatomy, University of Pittsburgh, Visiting Physician to St. Francis Hospital and the Tuberculosis Hospital, Pittsburgh, and Assistant Visiting Physician to the Western Pennsylvania Hospital. Address: 705 North Highland Avenue, Pittsburgh, Pa.

Dr. Rufus I. Cole has been appointed Director of the Rockefeller Hospital, New York City.

Dr. Robert L. Cunningham is Instructor in Physiology in the Los Angeles Department of Medicine of the University of California, and Resident Physician, Barlow Sanitarium, Los Angeles, Cal.

Dr. Sydney M. Cone is Professor of Pathology and Orthopedic Surgery at the Baltimore Medical College.

Dr. John Staige Davis is Visiting Surgeon at the Union Protestant Infirmary and the Church Home and Infirmary. Address: 1228 North Calvert Street, Baltimore.

Dr. J. Colton Deal is Assistant Surgeon in Dr. Joseph Price's Hospital for Women. His address is 3911 Locust Street, Philadelphia, Pa.

Dr. Ernest C. Dickson is Instructor in Pathology and Bacteriology, Cooper Medical College and Assistant Pathologist to the Lane Hospital and to the City and County Hospital, San Francisco, California.

Dr. Marshal Fabyan's address is 381 Commonwealth Avenue, Boston, Mass.

Dr. F. F. Gundrum is Resident Surgeon at St. Francis' Hospital, Pittsburgh, Pa.

Dr. L. P. Hamburger is Visiting Physician to the Church Home and Hebrew Hospital; Consulting Physician to the Children's Convalescent Home, and President of the Board of Directors, Jewish Home for Consumptives, Baltimore.

Dr. Frederic M. Hanes is Instructor in Pathology, Columbia University. Address: Livingston Hall, Columbia University, New York.

Dr. Henry Harris' address is 177 Post Street, San Francisco, Cal.

Dr. C. W. Hennington is on the Pathological Staff of the City Hospital, Rochester, N. Y. His address is 275 Alexander Street.

Dr. J. Gardner Hopkins is Assistant Pathologist to St. Luke's Hospital, New York City. Address: Amsterdam Avenue and 113th Street.

Dr. Guy L. Hunner is Professor of Gynecology, Women's Medical College, Visiting Gynecologist, Church Home and Infirmary, Hebrew Hospital, Hospital for the Women of Maryland and Good Samaritan Hospital, Baltimore; Frederick Hospital and Hagerstown Hospital, and Consulting Gynecologist to Brattleboro Memorial Hospital, Brattleboro, Vermont. His address is 2305 St. Paul Street, Baltimore.

Dr. Gerry R. Holden is Gynecologist to St. Luke's Hospital, Jacksonville, Fla. Address: 27 West Beaver Street.

Dr. Henry T. Hutchins is Surgeon to the Out-Patients, the Free Hospital for Women, Brookline, Mass.

Dr. H. L. Langnecker is Assistant to Orthopedic Surgeon, Massachusetts General Hospital. Address: 2 Mount Auburn Street, Cambridge, Mass.

Dr. Herbert M. Little is Lecturer in Obstetrics and Demonstrator in Gynecology, McGill University, Assistant Accoucheur to the Montreal Maternity and Assistant to the Gynecologist, The Montreal General Hospital. His address is 261 Peel Street, Montreal, Canada.

Dr. David R. Lyman is Clinical Lecturer on Tuberculosis, Yale Medical School. Address: 193 York Street, New Haven, or Gaylord Farm Sanitarium, Wallingford, Conn.

Dr. W. G. MacCallum is Professor of Pathology in Columbia University in the Departments of Medicine and Pure Science; and Pathologist to the German Hospital. His address is 437 West 59th Street, New York City.

Dr. J. D. Madison is Professor of Medicine, Medical Department, Carroll College, Milwaukee, Wis.

Dr. Carl R. Meloy is Adjunct Professor of Pathology, University of Virginia, and Pathologist to the University Hospital. Address: Charlottesville, Va.

Dr. G. Brown Miller is Associate in Gynecology in the George Washington University, Attending Gynecologist to the Emergency Hospital and Associate Gynecologist to the Columbia Hospital, Washington, D. C. Address: 1731 H St., N. W.

Dr. Robert T. Miller, Jr., is Visiting Surgeon to St. Francis Hospital, Pittsburgh. Address: Bellefield Dwellings, Pittsburgh, Pa.

Dr. W. Bean Moulton is Secretary of the Maine Medical Association. Address: 622 Congress Street, Portland, Maine.

Dr. Charles F. Nassau is Associate in Surgery, Jefferson Medical College; Surgeon to St. Joseph's Hospital; Surgeon-in-Chief, Frankford Hospital, Assistant Surgeon, Jefferson Medical College Hospital, and Surgeon to St. Vincents' Home. Address: 1831 Chestnut Street, Philadelphia, Pa.

Dr. W. O. Pauli is Demonstrator in Clinical Microscopy and Assistant Clinical Instructor in Obstetrics in the Ohio-Miami Medical College, Cincinnati, Ohio.

Dr. C. A. Penrose is Visiting Physician to the Church Home and Infirmary. His address is 21 West Mount Royal Avenue, Baltimore.

Dr. Theodore F. Riggs is Visiting Surgeon to St. Mary's Hospital, Pierre, S. D.

Dr. Stephen Rushmore is Visiting Gynecologist to the Carney Hospital, Boston, Mass.

Dr. Joseph T. Smith, Jr., is First Assistant Resident in Gynecology, Lakeside Hospital, Cleveland, O.

Dr. Walter Steiner is Visiting Physician to the Hartford Hospital, Consulting Physician to the Hartford Orphan Asylum, Hartford, Conn., and Consulting Physician to the Middlesex Hospital, Middletown, Conn.

Dr. A. Raymond Stevens is Adjunct Assistant Genito-Urinary Surgeon to Bellevue Hospital. His address is 14 East 58th Street, New York City.

Dr. Hugh A. Stewart is Adjunct Professor of Pathology, College of Physicians and Surgeons, Columbia University, New York. Address: Livingstone Hall.

Dr. Harvey B. Stone is Adjunct Professor of Surgery and Gynecology, University of Virginia.

Dr. H. J. Storrs is Instructor in Obstetrics in the Medical Department of Washington University, St. Louis, Mo. His address is 3720 Washington Boulevard.

Dr. S. Strouse is Assistant Pathologist, Michael Reese Hospital, Chicago.

Dr. Louis M. Warfield is Assistant Superintendent and Pathologist to the Milwaukee County Hospital. Address: Wauwatosa, Wis.

Dr. Stephen H. Watts is Professor of Surgery and Gynecology, University of Virginia, and Director of the University Hospital.

Dr. G. H. White is Pathologist to the Charleston General Hospital, Charleston, W. Va.

Dr. Harry I. Wiel is Assistant in Medicine in Charge of Tuberculosis Class, San Francisco Polyclinic. Address: Butler Building, San Francisco, Cal.

Dr. Otis B. Wight is Lecturer in Clinical Surgery, Medical Department, University of Oregon. His address is 903 Corbett Building, Portland, Ore.

Dr. J. Whitridge Williams is a member of the Board of Supervisors of City Charities, Baltimore.

Dr. Gordon Wilson is Associate Professor of the Practice of Medicine, University of Maryland; Chief Physician to Tuberculosis Clinic and Visiting Physician to the University of Maryland Hospital; Physician in Charge of the Municipal Tuberculosis Hospital; Examining Physician to the Maryland State Tuberculosis Sanitarium, and Visiting Physician to Eudowood Sanitarium. Address: 1318 North Charles Street.

Dr. Paul G. Woolley is Professor of Pathology, Ohio-Miami Medical College and Pathologist to the Cincinnati Hospital.

Dr. Douglas Vanderhoof is Attending Physician to the Memorial Hospital, Consulting Physician to the Johnston Hospital, Richmond, Va., and Editor of the Old Dominion Journal of Medicine and Surgery.

Dr. J. M. Taylor is President of the Idaho State Medical Society and an Associate Editor of Northwest Medicine.

HERTER LECTURES FOR 1910.

Professor Hans Chiari, Professor of Pathological Anatomy in the University of Strassburg, will deliver the next course of lectures on the Herter Foundation, on October 5, 6 and 7, 1910, in the Johns Hopkins Medical School. The subjects of the lectures will be:

(1) Ueber die Bedeutung des Amnions für die Missbildungen des Menschen.

(2) Pankreas nekrose.

(3) Spondylolisthesis.

The lectures will be in German.

NOTES ON NEW BOOKS.

Expansion of Races. By CHARLES EDWARD WOODRUFF, A. M., M. D. (*New York: Rebman Company, 1909.*)

Dr. Charles E. Woodruff has given the public in his book, "Expansion of Races," a large volume of 486 pages, in which he has traced the evolution of the human race from its earliest and most primitive sources down to the present time. The subject has been elaborately treated, and the author shows great knowledge of a science, certain parts of which he has studied at first-hand. The book begins with the remark that "man is under the influence of all natural laws governing the evolution, increase and spread of other species." That intelligence may have an influence in the process of evolution is admitted, but the author contends throughout his work that the brain of man is as much a material thing as the skull itself, and is controlled entirely by the laws of biology. The basic fact in Dr. Woodruff's book is that in the human race more individuals are born than can possibly survive to raise offspring of their own, and that the law which controls over-production is the ability of their native land to furnish food. The surplus population has to be killed off, either by accident or with deliberate purpose, and only the fittest for survival remain. Thus the balance is constantly maintained between the birth-rate and the death-rate, while in the struggle for existence alone does the species find its opportunity for improvement or evolution.

The table of contents gives a fair idea of how the main theme has been studied from every standpoint. Five chapters deal with the over-population of the world, which is termed the "saturation" of the earth, meaning thereby the covering of a given portion of land with as many people as the land can feed. The author's similes are taken from the action of water or of any fluid. Thus he speaks of the "spreading waves of living species"; the "population which flows sluggishly and slowly like lava"; or "the rivers of emigrating races following the channels which offer the least resistance and are guided by natural laws."

Dr. Woodruff's statements of fact are sustained by examples taken from different continents, also by tables of carefully compiled statistics. Thus, Canada and New England are quoted as illustrative of the fact that the opening up of new lands, a sudden increase in farming activities, or a marked improvement of the manner of irrigation will always be followed by an increase in the birth-rate, as the land becomes able to feed more people, while with a density of population or a high degree of civilization the population will remain the same, the land being taxed to its utmost capacity, either to feed the large numbers, or to produce food for exportation. China admirably illustrates a country where a dense population of about 400,000,000, having an equal ratio of one death to one birth, has remained stationary for many centuries. The influences which bear upon this subject are reviewed and analyzed. Foremost among these may be mentioned the tendency to emigration which always accompanies over-population. Dr. Woodruff classifies under the general term of emigration every notable outgoing of many people, like the Aryan exodus in the earliest times; the forcing out each year by the Romans of a certain number of their young men to seek new homes for themselves; and even the crusades, which he thinks may have been "explosions of restlessness" from an over-crowding at home.

Famines in countries where food is scarce, and famines in the lands of plenty but where the people are undeveloped and consequently ignorant and unskilled, are cited as the original cause for the starting of such emigrations. It is difficult at this point to entirely agree with the author, and we wonder if Dr. Woodruff might not seem unduly dogmatic in wanting us to believe, in accordance with his theory, that the Puritans, the Jesuits, the Dutch in Pennsylvania, the French Canadians, etc., as well as the many others who have come to this country to find freedom, either political, religious, social or solely personal, were in reality merely impelled by the scarcity of food at home.

War, epidemics, poverty and all disasters which destroy by wholesale large numbers of people, are declared a necessity on the ground that they are more reasonable and more humane than the common habit of infanticide among savages and the lower races and the consequent killing of the aged, the infirm and the disabled. Pestilences and diseases which come from over-crowding, and which in their turn help to limit over-saturation, are discussed at full length, especially tuberculosis, typhoid, typhus and the many sorts of plagues.

The evolution of man himself and his efforts to lift himself above the animals who contest with him for life, follows next in order. Accepting a questionable theory, Dr. Woodruff divides the human race into two main branches. The first one he declares originated in Central Europe, and has for its characteristic features an oval, long face, a long head (dolichocephalic), wiry or curly hair and an emotional temperament. Later he gives the distinctive name of *blond race* to this division. The other came from Central Asia, and has a broad face, a broad head (brachycephalic), straight hair and a phlegmatic, unemotional temperament. This race he calls the brunet type.

The date of man's origin is placed in the earliest glacial period, or 250,000 years ago, and an estimate of over a million years is made for the evolution of the anthropoid to the man. Human length of life has steadily increased since the time when the primitive savage was under the same necessity as the animals of never dying a natural death.

With a certain degree of civilization came the leisure from the actual struggle for existence, and man began to realize that life is valuable in itself and must be cared for. He voluntarily diminished the birth-rate in order to raise all of his children, and undertook the care and protection of the aged in order to profit by the wisdom, knowledge and experience which can only come with mature age and are among the luxuries demanded by civilization.

An interesting chapter is devoted to what the author calls the modern or nitrogen famine. It is at this point that Dr. Woodruff begins to show the results of some of his original investigations in the tropics, especially in the Philippines. He bears extensively on the results of eating food deficient in nitrogen, and the consequent decadence of the race due to defective development followed by the diseases peculiar to nitrogen starvation. The lower classes of China, Japan, and East India are excellent examples of insufficient nourishment, but we are less prepared for the warning which is given concerning the danger of adopting the present fad of low nitrogen diet.

Dr. Woodruff is well qualified to discuss the fate of all the conquering races in the tropics, and has a great deal to say regarding the myth of acclimatization. He gives some very good advice to settlers and travellers in the tropics, and disproves many fallacies concerning dietary measures usually adopted by the ignorant novice, such as the non-use of fats, of sugars and of meats, in hot climates. He advises a temperate use of alcohol, and insists upon the immediate adoption of certain habits which are commonly practiced by the natives.

The impossibility of complete acclimatization by the blond races leads Dr. Woodruff to assert that this is the reason why certain races which have been conquered, and have lived in complete subjugation for centuries, still retain their numerical force. White men cannot develop in zones of extreme heat or of extreme cold. The anemias of the tropics enfeeble and ultimately kill the

strongest adults. Their children cannot be raised to vigorous maturity unless sent back to the home country, and the second and third generations die out entirely. The original race alone persists, and its purity of blood is retained in a large measure by the hatred and obloquy heaped upon the hybrids or half-breeds—the conquering race always refusing to acknowledge them, and the natives treating them as outcasts. Under such circumstances they cannot thrive, but remain an undeveloped and impotent factor in the history of the race.

After having traced the evolution of man from his primitive condition to the present time, the social, racial, climatic and economic causes which have furthered the development of the race are elaborated with boldness and originality of thought. We learn the necessity of *commensalism*, or mutual aid between individuals first, and later between nations. Imperialism, or the national expansion is named a modern expression of the early emigration spirit. The chief causes for the present diminishing of birth-rates are attributed to modern marriage customs; prostitution, which eliminates a large percentage of women from child-bearing; abortions; the necessity for child labor and the poverty caused by large families.

The last part of the book is a short synopsis of the history of civilization from the primitive European races, the Greek and Roman civilizations, to the modern evolution of democracies. The problems of the Jews, Christianity, egoism and altruism are discussed, and the book ends with several chapters written in a prophetic manner concerning the future development of American democracy and the final solving of present governmental problems, such as those of the trusts, public service, the valuation of wages, unions and corporations, etc. The future of the human race, the question of the possibility of exhausting the present natural resources of the earth and how they may be replaced by other discoveries, are touched upon, while the future type of man and the brain of the coming world-nation is in part foretold.

In the hands of a less skilled writer this book would be in danger of losing its literary attraction, and degenerating from a work which cannot fail to be of wide and general interest, to a mere compilation of tables, statistics and reports, as well as epitomes of articles written on special economic or biologic subjects by the best scholars of America, England and Germany. The quotations are numberless, and the source of each reference is ably and accurately given. But Dr. Woodruff has managed to interject his personality through the whole and has kindled his dry facts with life and fire. With all his knowledge, and with his experience and interest in the human race, the pity is that he should disregard the fact that morals, esthetics, and religion come into play as factors in the evolution of man, so soon as the primitive barbaric periods are past. It is easy to say that "*we must not confuse natural laws with moral ideas*," but man does not grow like the plants or the animals, blindly following the laws of biology. He is swayed, influenced, molded and restrained by moral, sentimental and emotional considerations, and these must be taken into account.

Dr. Woodruff has a delicate, skilful touch, and can bend facts to fit his theories. Certainly his ideas are novel and unusual, and his readers will be surprised at his recasting of many old, established, and long accepted dictums. Alcoholism, for instance, he declares is no longer a universal evil. All the worst drunkards have been killed off long ago, and although more alcohol is used than ever before in the history of man, yet temperance is more general. Scotland and Wales might perhaps seem to be exceptions to this rule. And is it not true that habitual or "steady drinking" is in the end more harmful than repetitive drunkenness?

Prostitution as a necessary feature of social life, and its elevating influence on the female sex, even if it is at the expense of the health and vigor of the male sex, sounds unusual and unconvincing.

Although undeniably a fatalist, Dr. Woodruff is full of optimism for the future of the race, and points conclusively to the salient steps in the constant improvement of the world. He prophesies that the evolution will continue, and that as nature has produced higher types than Greece or Rome ever dreamed of, by the same process, in the future, exceptional varieties will appear with genius beyond our present comprehension.

His closing line reiterates in a single sentence the whole purpose of his book, namely that: "*Natural laws govern the world and all its inhabitants.*"

In closing we would like to add that in many instances throughout the book Dr. Woodruff is hardly fair to facts. For, as scientists recognize, there are no laws from without which entirely govern us. If this is true of physics and of biology, it is still more true of the evolution of civilization. Any "law" is only a statement of certain observed facts, a generalization of observations concerning the actions and reactions of certain forces. Even adamantine "laws," which a few years ago were considered invulnerable, have been abandoned by advanced thinkers. We, therefore, feel that it is to be regretted that the author should have attempted to load his theory with a needless materialism and fatalism. Yet, on the whole, we may greatly admire Dr. Woodruff's scholarship and industry and be grateful to him for his interesting book. G. M. G.

Those Nerves. By George Lincoln Walton, M. D., etc. (*Philadelphia and London: J. B. Lippincott Company, 1909.*)

Anyone who read "Why Worry," by the same author, and enjoyed the work, will get equal pleasure out of this new volume. Dr. Walton's philosophy is sound and his style not too didactic for the sufferers from nerves, who do not like to be preached to, and told to do this and that. He shows them in his frank and simple manner how they can help themselves, and in truth this little volume is one well worth reading by us all, for we are none of us absolutely healthy-minded, and may find suggestions in the book which will prove of real service.

Text-Book of Gynecological Diagnosis. By Georg Winter, O. O. Professor and Director of the Kgl. Universitäts-Frauenklinik in Königsberg, Prussia, with the collaboration of Dr. Carl Ruge, of Berlin. Edited by John G. Clark, M. D., Professor of Gynecology, University of Pennsylvania. After the Third Revised German Edition. Illustrated by five full page plates and three hundred and forty-six text illustrations in black and colors. (*Philadelphia and London: J. B. Lippincott Company, 1909.*)

In the preface to the first edition of this work, written in 1896, Professor Winter called attention to the tremendous strides which had been made in gynecological diagnosis and of the great value derived from the comparison of the palpatory findings before operation with the conditions revealed at operation. He believed, at that time, that gynecological diagnosis had become a science and a study of such importance that it demanded special treatment.

In the preface of the third edition, of which the present volume is a translation, he states that as gynecological diagnosis had developed greatly both clinically and pathologically, during the ten years since the second edition appeared, and as his own views of the subject had also changed he had found it necessary to revise the entire work. The greater part of the work was prepared by Professor Winter. Professor Carl Ruge contributed the part on microscopic diagnosis.

In the preface of the present edition, Dr. Clark states that, "In order to adopt this translation to American use, brief edi-

torial annotations have been made here and there, which have appeared essential to the wider adaptation of the book to this country. These comments are contained in separate editorial paragraphs, enclosed in brackets, thus leaving the translated German text intact."

The work is divided into three parts: General Diagnosis, Special Diagnosis and Analytical Diagnosis.

Under General Diagnosis the various methods of gynecological examinations are described and seventy-five pages are devoted to this subject.

The next five hundred and twenty-five pages, *i. e.*, the greater part of the work is devoted to Special Diagnosis. There is an excellent description of the "normal findings" as a foundation for the interpretation of pathological conditions—the topographic anatomy for the palpatory diagnosis and the normal histology for the microscopic diagnosis. This is followed by chapters on the following subjects: Diagnosis of Normal Pregnancy; Diagnosis of the Disturbances of Pregnancy; Microscopic Diagnosis of Pregnancy; Microscopic Diagnosis of the Membranes Expelled from Genitalia, Especially from the Uterus; Displacements of the Uterus and Adjacent Organs; Diagnosis of Uterine Myomata; Diagnosis of Ovarian Tumors; Diagnosis of Malignant Diseases of the Uterus; Neoplasma of the Vagina; Neoplasma and Ulcerations of the Vulva; Microscopic Diagnosis of Malignant Diseases of the Uterus, Vagina and Vulva; Microscopic Diagnosis of Polyps and Tissue Fragments from the Genitalia; Diagnosis of Tubal Diseases; Diagnosis of Pelvic Peritonitis; Diagnosis of Parametritis; Diagnosis of Uterine Catarrh; Microscopic Diagnosis of Endometritis; Diagnosis of Malformations of the Internal Genitalia; Diagnosis of Diseases of the Urinary Apparatus.

The plan of the special diagnosis of the various conditions is as follows: The pathological conditions are first described and these are followed by a description of the methods of examination best adapted for the diagnosis of each condition and especially what the palpatory findings should be; finally the differential diagnosis between it and conditions simulating it are given. The chapters on microscopic diagnosis are very thorough and well illustrated.

Under Analytical Diagnosis, the Causes of Hemorrhage, Amenorrhœa, Dysmenorrhœa, Sterility and Abdominal Tumors are given and methods of diagnosis are described.

This work represents the methods of diagnosis employed by one of the foremost German teachers with annotations from one of our own. As a third edition it also represents a thorough revision of a plan of teaching gynecological diagnosis used by the writer for several years and that plan is the description of the various pathological conditions present and then the demonstration of how a diagnosis should be made with especial emphasis on the palpatory findings present.

The book-making, including the index, is of the best, and the illustrations while not uniformly excellent, clearly show what they are intended to represent. The diagrammatic illustrations are particularly instructive.

To Dr. R. Max Goepp thanks are due for presenting us with a most excellent translation.

This book may be recommended not only to the student and general practitioner, but especially to the gynecologist, as it contains many points in the finer diagnoses of gynecological conditions which should be greatly appreciated by him. J. A. S.

Diseases of the Nose, Throat and Ear, Medical and Surgical. By William Lincoln Ballenger, M. D., etc. Second Edition, Revised and Enlarged. Illustrated. (*Philadelphia and New York: Lea & Febiger.*)

Diseases of the Nose, Throat and Ear. By Charles Huntoon Knight, M. D., etc., and W. Sohier Bryant, M. D., etc. Second Edition, Revised. Illustrated. Price $4.50. (*Philadelphia: P. Blakiston's Son & Co., 1909.*)

Clinical Manual for the Study of Diseases of the Throat. By James Walker Downie, M. B., F. F. P. S. G., etc. Second Edition, Revised and in Large Measure Rewritten. Illustrated. Price $3.25. (*Glasgow: James Maclehose & Sons, 1909.*)

All these three volumes, two by Americans and one by an Englishman, have appeared in their second editions within a short time of each other. Ballenger's work is the most comprehensive and largest, though Downie's, limited to the diseases of the throat, deals with those affections more fully than either of the others. The second edition of Ballenger is an improvement on the first, which was endorsed by us when it first appeared and we are glad to note that he no longer emphasizes the use of hydrozone, at least we do not find it referred to in the index. Further commendation of this excellent book is unnecessary. Although the work by Knight and Bryant is smaller than that of Ballenger, yet the nose, pharynx and larynx, and ear receive in relation one to the other about the same attention, the discussion of each occupying about a third of the volume. With these three volumes at hand, or any one of them, a student can gain a very satisfactory grasp of the diseases of the organs treated. Each is good and may be recommended without hesitation.

A Text-Book on the Principles and Practice of Surgery. By George Emerson Brewer, M. D., Professor of Clinical Surgery in the College of Physicians and Surgeons, New York. Octavo, 908 pages, 415 engravings and 14 full-page plates. Second Edition. Price $5.00. (*Philadelphia and New York: Lea & Febiger, 1909.*)

Dr. Brewer's position as one of the leading surgeons of America gives to this text-book an authority which at once makes it valuable to the student. It does not attempt to compete with the larger systems of surgery, but as a work in one volume is very complete and satisfactory. This edition, revised and enlarged, will, there is no question, receive the same and even greater approval than the first edition.

BOOKS RECEIVED.

Biographic Clinics. Volume VI. Essays Concerning the Influence of Visual Function; Pathologic and Physiologic, upon the Health of Patients. By George M. Gould, M. D. 1909. 12mo. 492 pages. P. Blakiston's Son & Co., Philadelphia.

American Association of Medical Milk Commissions. Proceedings of the Third Annual Conference held at Atlantic City, New Jersey, June 7, 1909. 8vo. 142 pages. Cincinnati, Ohio.

A Manual of the Working Methods and Standards for the Use of the Medical Milk Commission. 1909. 8vo. 24 pages. Compiled by the American Association of Medical Milk Commissions.

Functional Diagnosis. The Application of Physiology to Diagnosis. By Thomas G. Atkinson, M. D. [1909.] 12mo. 213 pages. Chicago Medical Book Company, Chicago.

Surgical Diagnosis. By Alexander Bryan Johnson, Ph. B., M. D. Volume III. The Spine. The Nerves. The Pelvis. The Extremities. Appendix. With one colored plate and two hundred and seventy-four illustrations in text. 1910. 8vo. 810 pages. D. Appleton & Co., New York and London.

The Medical Complications, Accidents and Sequels of Typhoid Fever and the Other Exanthemata. By Hobart Amory Hare, M. D., B. Sc., and E. J. G. Beardsley, M. D., L. R. C. P. (Lond.). With a Special Chapter on the Mental Disturbances Following Typhoid Fever by F. X. Dercum, M. D. With 26 illustrations and 2 plates. 1909. 8vo. 406 pages. Lea & Febiger, Philadelphia and New York.

Surgery of the Brain and Spinal Cord. Based on Personal Experiences. By Prof. Fedor Krause, M. D. Translated by Prof. Herman A. Haubold, M. D. Vol. 1. With 63 figures in the text, 24 colored plates and 1 half-tone plate. [1909.] 4to. 282 pages. Rebman Company, New York.

A System of Syphilis. In Six Volumes. Edited by D'Arcy Power, M. B. Oxon., F. R. C. S., and J. Keogh Murphy, M. D., M. C. Cantab., F. R. C. S. With an Introduction by Sir Jonathan Hutchinson, F. R. S. Volume III. 1909. 8vo. 279 pages. Oxford Medical Publications. Henry Frowde, London; Hodder & Stoughton, London.

Bacteriology for Nurses. By Isabel McIsaac. 1909. 12mo. 179 pages. The Macmillan Company, New York.

Sammlung Anatomischer und Physiologischer Vorträge und Aufsätze. Herausgegeben von Prof. Dr. E. Gaupp und Prof. Dr. W. Nagel. Heft 6. Die ortsfremden Epithelgewebe des Menschen. Untersuchungen und Betrachtungen. Von Dr. Herm. Schridde. Mit 21 Figuren im Text. 1909. 8vo. 63 pages. Gustav Fischer, Jena.

Le Rhumatisme Tuberculeux. Par A. Poncet et R. Leriche. Avec 46 figures dans le texte. 1909. 16mo. 285 pages. Octave Doin et Fils, Paris.

Transactions of the American Surgical Association. Volume the twenty-seventh. Edited by Richard H. Harte, M. D., Recorder of the Association. 1909. 8vo. 634 pages. Printed for the Association. Philadelphia.

Transactions of the American Gynecological Society. Volume thirty-four. For the year 1909. 8vo. 876 pages. Wm. J. Dornan, Printer, Philadelphia.

Verhandlungen der Deutschen Gesellschaft für Chirurgie. Achtunddreissigster Congress, Abgehalten zu Berlin, 14-17 April, 1909. Mit 7 Tafeln und Textfiguren. 8vo. 856 pages. August Hirschwald, Berlin.

A System of Operative Surgery. By Various Authors. Edited by F. F. Burghard, M. S. (Lond.), F. R. C. S. (Eng.). Volume II. Operations for Tuberculous Affections of the Bones and Joints. Operations upon the Lips, Face and Jaws, etc. 1909. 8vo. 720 pages. Oxford Medical Publications. Henry Frowde, London; Hodder & Stoughton, London.

Parenthood and Race Culture. An Outline of Eugenics. By Caleb Williams Salleeby, M. D., Ch. B., F. Z. R. (Edin.). 1909. 8vo. 389 pages. Moffat, Yard & Co., New York.

Transactions of the American Dermatological Association. Thirty-second Annual Meeting held in Annapolis, Maryland, Sept. 24-25, and in Baltimore, Sept. 26, 1908. 8vo. 287 pages.

Atlas of External Diseases of the Eye. By Dr. Richard Greeff. Only Authorized English Translation by P. W. Shedd, M. D. With 84 illustrations in color from wax models printed on 54 plates with explanatory text. The illustrations are from models in the Pathoplastic Institute in Berlin. Art Director: F. Kolbow. 1909. 4to. 140 pages. Rebman Company, New York.

Practical Points in the Use of X-rays and High Frequency Currents. By Aspinwall Judd, M. D. 1909. 12mo. 189 pages. Rebman Company, New York.

Renal, Ureteral, Perirenal and Adrenal Tumors and Actinomycosis and Echinococcus of the Kidney. By Edgar Garceau, M. D. With seventy-two illustrations in text. 1909. 8vo. 421 pages. D. Appleton & Co., New York and London.

Chemical and Microscopical Diagnosis. By Francis Carter Wood, M. D. Second edition. With one hundred and ninety-two illustrations in the text and nine colored plates. 1909. 8vo. 767 pages. D. Appleton & Co., New York and London.

Studies in Rabies. Collected Writings of Nathaniel Garland Keirle, A. M., M. D., D. Sc. With an Introduction by William H. Welch and a Biographical Sketch by Harry Friedenwald. Testimonial Edition. 1909. 8vo. 386 pages. The Lord Baltimore Press, Baltimore.

The Principles of Pathology. By J. George Adami, M. A., LL. D., F. R. S., and Albert G. Nicholls, M. A., M. D., D. Sc., F. R. S. (Can.). Volume II, Systemic Pathology. With 310 engravings and 15 plates. 1909. 8vo. 1082 pages. Lea & Febiger, Philadelphia and New York.

Transactions of the American Urological Association. Sixth Annual Meeting, Atlantic City, N. J., June 3 and 4, 1907. Edited by Charles Greene Cumston, M. D. 1908. 8vo. 235 pages. Printed for the Association at the Riverside Press, Brookline, Massachusetts.

Transactions of the American Urological Association. Seventh Annual Meeting at Chicago, Illinois, June 1 and 2, 1908. Edited by Charles Greene Cumston, M. D. 1909. 8vo. 276 pages. Printed for the Association at the Riverside Press, Brookline, Massachusetts.

The Mode of Infection and Duration of the Infectious Period in Scarlet Fever. By Charles V. Chapin, M. D. Fiske Fund Prize Dissertation. No. LII. 1909. 8vo. 52 pages. Snow & Farhnam Company, Printers, Providence.

Those Nerves. By George Lincoln Walton. 1909. 12mo. 203 pages. J. B. Lippincott Company, Philadelphia and London.

Introduction to Practical Chemistry. For Medical, Dental and General Students. By A. M. Kellas, B. Sc. (Lond.), Ph. D. (Heidelberg). Oxford Medical Publications. 1909. 8vo. 262 pages. Henry Frowde, London; Hodder & Stoughton, London.

Diseases of the Nose, Throat and Ear. Medical and Surgical. By William Lincoln Ballenger, M. D. Second edition, revised and enlarged. Illustrated with 491 engravings and 17 plates. 1909. 8vo. 932 pages. Lea & Febiger, Philadelphia and New York.

Diseases of the Nose, Throat and Ear. By Charles Huntoon Knight, A. M., M. D., and W. Sohier Bryant, A. M., M. D. Second edition, revised. With 239 illustrations. P. Blakiston's Son & Co., Philadelphia.

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CONTENTS.

A PRELIMINARY REPORT OF SOME CASES OF PURPURA HÆMORRHAGICA DUE TO BENZOL POISONING.

By L. Selling, M. D.

(From the Pathological Laboratory of the Johns Hopkins Hospital.)

The cases which we have to report belong clinically to the group of purpuras; and from the mode of occurrence and from the results of the experimental work it is probable that they belong to the group of toxic purpuras. They occurred at a factory, in the suburbs of Baltimore, engaged in the manufacture of tin cans.

The factory is of fair size, employing about 325 hands and divided into several departments. The cases were not distributed uniformly throughout the factory, but were confined to one department, in fact, to one room of that department, the so-called "coating room." The only essential difference in the processes as carried on here and in the rest of the factory consisted in the use of a substitute for solder; a mixture composed of pure rubber, a rosin, and a coloring matter, dissolved in commercial benzol. Twenty-three hands were employed in the coating room; five men as machinists, four girls as inspectors, and fourteen girls, between the ages of 14 and 16, at the coating machines themselves. It is among these last that most of the cases, and all of the serious cases, occurred.

Their work was easy. One-half of them had simply to feed the can covers to the machines, which automatically carried them around and coated them about the margin with a thin layer of the pasty solution, whose constitution has been described, while the other half removed the coated covers. The covers were then piled in trays, inspected, and allowed to dry by the evaporation of the benzol. Ten gallons of benzol a day were used and allowed to evaporate in this room. In spite of the wide open windows and excellent ventilation—the cases occurred in summer—the space immediately about the coating machines was pervaded by a well-marked odor of benzol, while the same odor, much weaker, was noticeable throughout the rest of the room.

Case I.—M. W., white, female, aet. 14 yrs. Occupation: Factory hand.

The patient was first seen by Dr. Girdwood about June 1, 1909. At that time he was treating the mother for pneumonia and his attention was called to the daughter incidentally by her marked pallor and by the presence of a purpuric eruption. She was feeling perfectly well. Shortly after this she began to have hæmorrhages from the mouth and nose and she was advised by Dr. Girdwood to enter the hospital.

She was admitted to the Johns Hopkins Hospital June 28, 1909, complaining of "spots on body and dizziness."

Family History.—One uncle died of tuberculosis.

Past History.—Negative except for mumps, chicken-pox, and two attacks of measles. She had been working in the canning company for about four months at the coating machines. During this period she had no symptoms whatever and stopped work because of her mother's illness.

Present Illness.—The patient dates the present illness from the latter part of May, 1909, about one month before admission, when she first noticed blue spots on her arms and legs. These, she states, came out slowly and a few at a time. Shortly after this, she began to have bleeding from the gums, nose, and throat, one attack of epistaxis lasting two days. A few days before admission there was a very severe hæmorrhage from the throat, controlled only with difficulty by local applications. For the past week she has been in bed, the chief symptoms being weakness and dizziness. There have been no joint pains and no gastro-intestinal symptoms.

Physical Examination on Admission.—Patient is a well built, well nourished girl. Skin shows a marked waxy pallor and mucous membranes are very pale. Scattered over the arms and legs and, to a less extent, over the trunk are purplish-red to blue macules, 1 to 3 mm. in diameter and which do not change on pressure. Several fading spots are present on the face. On the right shin there is a large ecchymosis and a similar, but smaller one, on the left shin. The gums show slight bleeding, especially about the root of a broken tooth. They are not spongy. In the region of the left tonsil and the right anterior pillar and extending up to the uvula is a dark brown necrotic looking mass surrounded by an inflamed border. This was the site of a severe hæmorrhage which had been controlled by the application of ferrous sulphate before admission. No glandular enlargement.

Heart.—Negative except for systolic murmur over precordium, which was considered of hemic origin. Lungs negative.

Abdomen.—Liver edge easily felt 2 cm. below costal margin in right mammillary line; edge sharp and soft. Spleen not felt; dulness not increased. No œdema of legs.

Ophthalmoscopic Examination.—Moderate grade of neuro-retinal œdema. Fundi very pale and flecked throughout by great numbers of hæmorrhages, linear and round. These are especially numerous about the discs. The arteries are extremely pale. The veins are pale but relatively darker than the arteries.

For the first few days after admission the patient was listless, but, in spite of the marked anæmia, her condition seemed very good. There was a continuous, but slight, oozing from the mouth and throat, with an occasional expectoration of a blood clot. A few fresh purpuric spots appeared, some of them on the gums.

On July 3, the patient became very toxic. She was in a state of stupor from which she could not be aroused. The pulse was small and weak. Because of the seriousness of her condition, a transfusion of blood was attempted, following which the pulse became fuller and of a better quality and the mucous membranes of a slightly better color. There was, however, no change in the blood count.

July 4. The condition was much improved. The patient was mentally clear. The pulse slower and of better quality. The improvement continued until July 6, when she lapsed back into the previous toxic state. The respiration was rapid and labored, pulse rapid and of poor quality. She became steadily weaker until the exitus which occurred on that day.

During her stay in the hospital the temperature ranged from 99.8° to 104.6° F., the pulse from 108 to 165 per minute. Blood culture and Widal negative.

The urine was normal on admission, but following the transfusion showed albumin and a few hyaline and granular casts. There was no evidence of hemolysis either in the change in the color of the urine or in the appearance of jaundice.

Blood on Admission.—The examination of the fresh blood showed the red cells smaller than normal, pale and with very pale centres; moderate anisocytosis, but no extremely large or small forms. No poikilocytosis. Marked leucopænia with predominance of mononuclears.

	R. B. C.	W. B. C.	Hgb.
June 28	———	1,280	28% (Sahli)
July 1	1,090,000	480	11%
July 3	800,000	480	—
July 4	640,000	600	8%

In all the fresh smears examined, platelets were practically absent. Coagulation time 4½ minutes.

Differential count of smears made July 3: (Ehrlich's triacid stain.)

Polymorphonuclears	43%
Lymphocytes	41%
Large mononuclears	14%
Unclassified	2%

100 cells were counted. One megaloblast was seen; no normoblasts.

Contraction of the Blood Clot.—The blood, drawn from the ear and allowed to stand in a tube for 24 hours, showed some contraction of the clot and expression of the serum. The extent of contraction, however, and the amount of serum expressed were distinctly less than in the control tubes taken from normal patients.

Autopsy (abstract) by Dr. W. G. MacCallum. Anatomical diagnosis: Purpura hæmorrhagica (probably toxic); hæmorrhages in the skin, viscera, and serous surfaces; pallor of the organs.

Muscles a deep red color. Blood pale and watery. The heart muscle, and to a less extent, the liver, show some fatty degeneration.

Bone Marrow.—The bone marrow of the femur is fairly consistent; it is of a dull ochre yellow color with no abundance of blood supply. It does not look like a markedly hyperplastic marrow.

Microscopic Report.—Malpighian corpuscles of the spleen show areas of hyaline necrosis. Otherwise the findings simply confirm the gross description.

Bone marrow, microscopic examination by Dr. Boggs. Smear from the femur marrow (Romanowski stain) shows very few cells of any kind. The predominant cell is the normal red, which is pallid and slightly basophilic and shows no great irregularity. Leucocytes are extremely scanty. They are mostly of the lymphocytic or myeloblastic type. They are characterised generally by a very definitely reduced chromatin in the nuclei. Many nuclei show vacuolization and the cytoplasm is thin, fragile and poorly stained. One megalocaryocyte seen on fairly careful examination of the cover slip. Suggests an aplastic bone marrow.

Case II.—F. C., white, female, aet., 14 yrs. Occupation: Factory hand.

Admitted to the Johns Hopkins Hospital, July 6, 1909, complaining of spots on body and pain in the side.

The history, physical examination and the course in this case were so similar to those in the preceding that a detailed description is unnecessary.

She had been working in the factory for five months and had had symptoms for only one week. Previous to that she had felt perfectly well.

Blood Examination.—On admission the fresh blood showed the red cells of fair color with a very few pessary forms and a slight grade of anisocytosis. No poikilocytosis.

	R. B. C.	W. B. C.	Hgb.
July 6	2,100,000	560	37% (Sahli)
July 8	2,100,000	——	28%
July 9	————	360	—
July 12	1,150,000	140	15%

Differential count of smears taken July 6. (Ehrlich's triacid stain):

Polymorphonuclears	16%
Lymphocytes	71%
Large mononuclears	10%
Eosinophiles	2%
Unclassified	1%

Only 100 cells were counted, owing to the scarcity of leucocytes.

A platelet count (Pratt's method), on July 9, gave 2500 platelets per cubic centimetre.

Blood taken from the ear and allowed to stand in tube for 48 hours showed absolutely no expression of serum. Control tubes from other patients reacted normally.

Autopsy (abstract) by Dr. Winternitz. Anatomical diagnosis: Purpura hæmorrhagica; hæmorrhages in the skin, viscera and serous surfaces; pallor of the organs; hyperplasia of the bone marrow; acute pleurisy.

The muscles are deep red in color, suggesting the presence of methemoglobin. Slight fatty degeneration of the heart.

The Bone Marrow.—The marrow of the long bones is deep red in color and shows marked hyperplasia. Its redness, however, is different from that generally seen in hyperplastic marrow. It is rather deeper, darker red, having the same hue described for the muscles. Smears taken from this marrow show not a hyperplastic, but an aplastic condition. The appearance closely resembles that of the bone marrow in Case I, with the exception that the reduction in the cellular elements had not reached quite so marked a grade.

CASE III.—A. N., white, female, aet., 14 yrs. Occupation: Factory hand.

Admitted to the Johns Hopkins Hospital, July 6, 1909, complaining of giddy spells and stomach-ache.

Patient had been working at the canning company for about three months, in the coating room. She had had symptoms for two months. These were chiefly anorexia, abdominal pain, vomiting and headache, and one or two fainting spells. The purpuric eruption in this case was very much less extensive than in the preceding cases. The general condition of the patient throughout her stay in the hospital was excellent. At no time did she show any alarming symptoms. She was discharged after six days and has continued well since.

The Blood Examination.—The blood examination shows the red cells practically normal in appearance.

	R. B. C.	W. B. C.	Hgb.
July 6	4,900,000	4,400	54%
July 10	4,740,000	5,800	50%

Coagulation time 6½ minutes.

Platelet Count.—104,000 per cubic centimetres. Clotting of blood and expression of serum diminished as in the other cases.

An examination of the other employees working in the coating room was undertaken, and four were found, two men and two girls, who showed a few purpuric spots. They were entirely free from symptoms. Their blood showed a slight grade of anæmia and a leucocyte count varying from 3900 to 5200 per cmm., that is, either subnormal or on the lower limits of normal. Control counts taken from those working in other parts of the factory gave the white blood cells 5200 to 6000, and red blood cells 4,000,000 to 5,000,000 per cmm.

A series of cases of almost exactly the same character was reported by Santesson,[1] of Stockholm, in 1897. The cases occurred at a factory in Upsala engaged in the manufacture of bicycle tires, and where benzol was used as a solvent for rubber. His cases showed a marked purpuric eruption and four of them terminated fatally.

So we have two series of cases of purpura, some purpura hæmorrhagica, and some purpura simplex, with all the clinical features of the idiopathic purpuras; even to the diminution in platelets and in the expression of serum from the clotted blood. Both series occurred in factories where benzol was used as a solvent for rubber. The cases were chiefly among young girls and the course was essentially chronic, although in the end the serious symptoms developed suddenly. It is noteworthy, also, that the disease progressed in spite of withdrawal from the influence of the toxic agent.

The most remarkable feature was the blood condition, and this can be best described as the picture of an aplastic anæmia. In common with the aplastic anæmia were, *First,* the presence of only slight changes in the appearance of the red blood cells. These showed, in our cases, only slight pallor and slight anisocytosis. *Second,* the absence of regenerative forms. In stained specimens of the two fatal cases, only one megaloblast and no normoblasts were found. *Third,* scantiness of platelets. *Fourth,* diminution of the granular types of white blood cells, with a relative increase in the mononuclear elements. In our Case I, polymorphonuclears were reduced to 43% while mononuclears were 55%. In Case II, the polymorphonuclears were 18% and the mononuclears 81%. *Fifth,* leucopænia. This reached a much more striking grade in our cases than in any of the reported cases of aplastic anæmia. In Case I, there was a count of 1280 cells on admission and later of 460 cells. In Case II, there were 550 cells on admission and on day of death the count had fallen to 140 cells per cmm. Similarly one of Santesson's cases showed, with a red blood count of 3,700,000, no white cells in the squares of the counting chamber, and only 5 to 10 around the margin of the disc.

In attempting to locate the source of the trouble, Santesson performed some experiments with benzol and benzene. Before discussing his work a few words with regard to these substances will not be out of place because a similarity of names has given rise to great confusion in the literature.

We have to consider three substances: Benzene, benzol, and benzine. *Benzene* is a chemical substance of definite and known constitution, C_6H_6 the ordinary benzene ring. The term *benzol* is used in two senses; first, as a synonym for

[1] Santesson: Archiv für Hygiene, Vol. XXI, 1897, p. 336.

benzene, and second, to designate a rather complex mixture of variable composition derived from the distillation of coal tar. I think we can make it plain by indicating the derivation.

The fractional distillation of coal tar yields primarily four products:

1. Crude naphtha distilling below 180° C.
2. Dead oils or creasote oils distilling from 180° to 270° C.
3. Green or anthracene oil distilling above 270° C.
4. Pitch, the residue.

It is from the first fraction that commercial benzol is obtained by redistillation and purification. The benzols of the market vary widely in composition according to the source from which they are derived and the extent of purification. In general, they consist chiefly of benzene and its homologues (Toluene, $C_6H_5 \cdot CH_3$, and Xylene, $C_6H_4 \cdot (CH_3)_2$) together with small percentages of carbon disulphid, pentane C_5H_{12}, thiophene C_4H_4S and its homologues, traces of water, acetylene and impurities of indefinite nature.[2] *Benzine* with which these two have been confused, is a derivative, not of coal tar, but of petroleum. It is composed of some of the lighter materials obtained from crude petroleum on distillation, and consists essentially of hexane, C_6H_{14}, and heptane, C_7H_{16}; usually it contains no benzene, C_6H_6.

Santesson tried the action of benzol and chemically pure benzene on rabbits by subcutaneous injection and by wrapping the bodies of the animals in cloths soaked with the material. In this way he produced chronic poisoning and in nearly all of his cases found at autopsy hæmorrhages in the pleura, lungs, mucosa of the stomach and intestine, and once beneath the pericardium. Similar hæmorrhages have been found by other workers with more or less regularity, in animals poisoned with benzol, and they have also been found in several cases of poisoning in man, that have come to autopsy. L. Lewin considers them characteristic.[3]

Subsequently, Santesson[4] performed further experiments based on the finding, in one of his fatal cases, of a marked grade of fatty degeneration of the organs. Although realizing that this may have been due to the anæmia itself, he attempted to reproduce the condition in rabbits, and succeeded. On the basis of the hæmorrhages and the fatty degeneration of the organs he concluded that benzol was the source of poisoning, and in as much as he could produce the same changes with benzene, that benzene was the essential toxic agent.

Our own work has been directed along somewhat different lines, although using the same substances. A priori, we felt that we could exclude the pure rubber, the rosin, and the coloring matter, which consisted simply of a clay highly colored with iron oxide, and turned our attention to the solvent. An analysis by Dr. C. Glaser, for the factory, revealed the presence of traces of carbon disulphid, thiophene, and of nitrobenzol; the last present in quantities of only one milligram per litre.

An analysis was made by Dr. Penniman, for the Maryland State Board of Health, by subjecting the entire mixture as used at the factory, to fractional distillation and dividing it into ten equal fractions. The first fraction started to distill at 70.6° C. and ended at 80.5° C. The next eight fractions distilled at 80.5° C., and the last was taken without further treatment. The boiling point of pure benzene is 80.5° C., so this formed more than 80% of the solvent. The first, fifth, and tenth fractions were injected into rabbits in doses suitable to produce chronic or subacute poisoning, 1 to 3 ccm. in olive oil. The effects were *identical* with the *three,* and, as far as our experiments are concerned, this excludes nitrobenzol from any share in the results. Nitro-benzol has a boiling point of from 203° C., to 209° C., so that any present in the original mixture would have been found *only* in the last fraction. Carbon disulphid in the quantities present could have played no part.

After a variable interval of from one to eight days the white blood cells began to diminish in number and in one case a count of 20 cells per cmm. was obtained. In the early stages of the poisoning there was an outpouring of a large number of abnormal elements among the white cells, either typical large lymphocytes with a large, deeply staining nucleus and a small amount of very basophilic protoplasm or closely related cells which showed a varying degree of basophilia of the protoplasm and irregularities in the nucleus. Myelocytes were not found except in one case. When the leucopænia reached such a low grade as above described, death occurred, even if the injections were stopped. The fall in the red blood cells was much less marked than the fall in the leucocytes; counts below 4,000,000 per cmm. being very uncommon. By carrying the poisoning over a much longer period, however, we succeeded in producing in one case a high grade of anæmia, with about 1,500,000 red cells. Many nucleated reds appeared in this experiment.

The autopsy findings in our experiments with respect to hæmorrhages were practically negative. In only one or two did we find any at all, and these were in the gastric mucosa. The bone marrow, in the examination of which we received much assistance from Dr. Whipple, showed striking changes. In cases that had rapidly developed an extreme leucopænia the marrow showed marked aplasia. The polymorphonuclears had been almost wholly swept out and a large percentage of the myelocytes showed marked signs of degeneration, while all forms of white cells were greatly reduced. The red cells, on the other hand, were practically uninjured, showing no signs of degeneration.

The bone marrow picture showed striking resemblances to the bone marrow of our two fatal cases. In both it was the white cells especially that suffered and of the white cells mainly the granular elements. In contrast to this is the picture obtained after toluene poisoning. In experiments carried on with this substance we found likewise a destruction of white blood cells, as evidenced by the primary reduction in their number and by the appearance of abnormal elements

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[2] Allen: Commercial Organic Analysis. Vol. II, Part II, p. 176.

[3] Lewin: Münch. med. Wchnschr., LIV, II, 1907, p. 2733.

[4] Santesson: Skandanavisches Arch. f. Phys., Vol. X, 1900, p. 1.

among them in the circulating blood. In comparison with benzene, however, its action is feeble and the bone marrow is fully able to compensate the destruction. To meet the extra demands it must do extra work and, therefore, we find at autopsy a marked hyperplasia of the marrow, the fat being entirely replaced by an overgrowth of cells.

Experiments with chemically pure benzene yielded results identical with benzol, that is, leucopænia and aplasia of the bone marrow, and we have thus in benzene an intense poison for the white cells[5] of the blood. Its action on the red cells is much less marked. That there is some destruction here, too, is evidenced by an abnormal pigmentation of the spleen.

Finally the question arises whether we have actually demonstrated the toxic agent. The facts stand thus: first, the cases occurred only in that room of the factory where the benzol rubber solution was used. Second, similar cases have been reported in another factory where the benzol was used as a solvent for rubber. Third, the main features of the cases were purpura, anæmia, and leucopænia. Fourth, in the experiments with the benzol used at the factory we reproduced the leucopænia and in those directed toward that end, also the anæmia, that is two of the three chief symptoms; while others working with benzol have found evidence that it tends to produce hæmorrhages in different parts of the body. Fifth, benzene produces the same effect as benzol.

In closing we wish to express our thanks to Dr. L. F. Barker for permission to report these cases and to Dr. Boggs, Dr. Whipple, and Dr. Winternitz for their kind assistance, and to Dr. Price of the Maryland State Board of Health.

[5] Exposure to Roentgen Rays is likewise able to produce an enormous destruction of white cells.

ANERYTHRÆMIC ERYTHRÆMIA (?)

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(*From the Medical Clinic.*)

During the last two years I have had under observation in the dispensary of the Johns Hopkins Hospital two interesting patients. Their histories were somewhat similar, and further similarity was strikingly present in their physical conditions. Without a blood count, the diagnosis of erythræmia was immediately suggested. But, as the following notes show, this could not be definitely established:

Case I.—*Clinical Diagnosis.*—Anerythræmic erythræmia (?); epilepsy. A. H. (Dispensary No. E15,726), Austrian Hebrew, aet. 17, single, a clerk by occupation, was admitted to the Medical Dispensary, November 26, 1907, complaining of "nervous dyspepsia."

Family History.—(The following history was obtained at a later date with the aid of the patient's father:) Father and mother living; both complain of "stomach trouble" at times, but are otherwise well. A brother and a sister are well. No epilepsy or other nervous disease in the family. No tuberculosis.

Past History.—At the age of 1½ years the patient had "typhoid fever" in Austria; he was ill two months. At three he had "scarlet fever" and "diphtheria" in this country; good recovery. "Measles" at six. No other infectious diseases or fevers. No history of syphilis in parents. Patient denies exposure to venereal disease. No malaria.

Present Illness.—At the age of four the patient was seized with a general convulsion and loss of consciousness for 8 to 10 hours, the father says. Since then the attacks have been repeated at intervals varying from three to four days to a month. The patient says he is always warned of an oncoming attack by the fact that his "heart begins to hammer" for about a minute. His father says he has convulsions in some of his attacks, affecting the arms and legs, with grinding of the teeth. The patient "foams at the mouth and there is a rattling in the chest." The lips and face are always intensely blue during an attack; the patient says he has noticed blueness of the lips and face himself between the attacks, especially in the winter. He has bitten his tongue and passed urine and fæces involuntarily in some of the attacks. Following the attack he has headache and feels stupid for several hours. Milder attacks without convulsions are more frequent than the severe ones. In the former the same aura is noted; then the patient loses consciousness, and, if he happens to be on the street, he drops anything he may be carrying and may go four to six blocks without having any recollection of what he has done. Constipation has always seemed to bear a definite relationship to the attacks, the latter being more frequent when he is constipated. He frequently has slight vertigo and occasionally vomits. He has been constipated and has had to take laxative medicines since the attacks first began. The father has never noticed that the patient's face grew blue in cold weather, and the patient himself cannot say how long he has noticed it.

Status præsens.—No abnormality was noted on the day of admission, but this is probably accounted for by the fact that there was not sufficient time for a careful examination. I saw the patient for the first time December 28, 1907. At this time his lips were very cyanotic, his face and extremities less so. There was a diffuse cyanosis of the trunk of slight degree. The heart and lungs were negative.

The abdomen looked natural. The spleen was readily felt with the patient on his back breathing quietly; it extended about one finger-breadth below the costal margin, and its edge was firm and rounded. No enlargement of the liver could be demonstrated.

Blood examination made at this time showed 4,880,000 red blood cells and 89% hæmoglobin (Sahli).

The patient said he had never had malaria, but vertigo had troubled him for about five years.

March 4, 1908. Has had several attacks of petit mal. He has been taking laxatives and tonics.

R. b. c.	4,910,000
W. b. c.	12,000
Hb.	89% (Sahli)

Differential count of 628 white cells (Wilson's stain) gave: Lymphocytes 27.2%; large mononuclears and transitionals 3.3%; polymorphonuclear neutrophiles 60.3%; eosinophiles 7.9%; mast

cells 0.8%; neutrophilic myelocytes 0.16%; degenerated forms 0.3%. No alterations in the red cells were seen. Platelets were about normal in number. No malarial parasites were seen. No cause of the eosinophilia, such as skin disease, asthma, intestinal parasites, trichinosis, has been found.

March 7, 1908. *Blood* examined for the bands of methæmoglobin and sulph-hæmoglobin gave a negative result.

May 6, 1908. Cyanosis of lips and ears well marked. Hb. = 91% (Sahli). *Spectroscopic examination* of the blood again negative.

November 10, 1909. The patient was requested to return to the clinic for examination. He says he has felt better, on the whole, during the last eighteen months. The bowels have been kept open. He has had attacks of vertigo once in three or four weeks (evidently petit mal, according to the description given by his father), but in the last month two attacks have occurred. In January, 1909, the patient was in bed for a week and suffered with vertigo, drowsiness, and nausea.

The patient was shown by Dr. T. McCrae to a clinic for the students and the following is a brief abstract of his remarks: The patient is well nourished. The lips and ears have a bluish tint. Tongue clean. Mucous membranes good color. No jaundice.

Heart and lungs clear.

Abdomen tense. Spleen enlarged and firm, one inch below the costal margin. Abdomen otherwise negative.

In discussing the case, Dr. McCrae called attention to the fact that there was no evidence of leukæmia, malaria, lues, new growth, amyloid disease, typhoid fever, or splenic anæmia, and expressed the opinion that the case was probably an early erythræmia.

November 10, 1909. *Urine;* fresh specimen: Clear, yellow, acid, sp. gr. 1.013. No albumin or sugar. Urobilinogen—trace. Urobilin—negative with Schlesinger's test after addition of Lugol's solution. Sediment—none.

Blood.—R. b. c. 5,104,000; w. b. c. 5,600; hb. 107% (Sahli). Differential count of only 233 cells (Wilson's stain) gave: Lymphocytes 34.7%; large mononuclears and transitionals 4.7%; polymorphonuclear neutrophiles 56.2%; eosinophiles 1.7%; mast cells 0.82%; myelocytes 0.43%; degenerated forms 1.3%. No abnormalities in the red cells; platelets about normal.

November 22, 1909. No attacks of epilepsy in the last two weeks, but several spells of nausea and vertigo. Complains of burning of the lips. The patient has been taking Fowler's solution and calcium lactate.

Stool (fresh).—Normal color and odor; soft. Nothing abnormal was found on gross or microscopic examination. No parasites or ova.

Blood.—R. b. c. 5,000,000; w. b. c. 4,000; hb. 105% (Sahli). *Viscosity* of the blood (Dr. Austrian) = 5. Spectroscopic examination of the blood (kindly verified by Professor Abel) was negative for sulph-hæmoglobin and methæmoglobin. Differential count of 542 cells (Ehrlich's triacid stain) gave: Lymphocytes 25.2%; large mononuclears and transitionals 3.8% (of which about 1.1% were Rieder cells); polymorphonuclear neutrophiles 64.0%; eosinophiles 3.7%; mast cells 0.73%; myelocytes 0.73%; degenerated forms 1.6%. No nucleated reds, etc.

Dr. Forster, of the Phipps Dispensary, kindly examined the patient's lungs, before giving him the tuberculin test, and found the percussion note on each side good; breath sounds good. No râles heard anywhere, even after cough. Result: Normal lungs. The *tuberculin test* showed a positive von Pirquet, a negative ophthalmo-reaction after instillation of 1% and 5% old tuberculin, practically excluding an active lesion (Dr. Hamman).

Case II.—*Clinical Diagnosis.*—Anerythræmic erythræmia (?).

K. H. (Dispensary No. E21,877), Russian Hebrew, aet. 21, single, a tailor, was admitted to the Medical Dispensary, April 1, 1908, complaining of "constipation and pain in the chest."

Family History.—Unimportant.

Past History.—Unimportant. Has always been well until the present illness. The patient denies venereal disease, and says that "whooping-cough" is the only disease he has had.

Present Illness.—Two years ago the patient was troubled with "giddiness in the head" and pain in the left chest in the region of the heart. He remained in bed for two months, recovered, and remained well for a year, when the trouble returned. The patient is not constantly ill, as he was at the onset. Some days he feels perfectly well; on others he complains of giddiness, nausea, and pain in the left chest. The vertigo comes on especially after meals, although he has noticed it at times before breakfast. Usually the symptoms are relieved by taking a dose of Epsom salts. The pain in the chest is quite constant, and at times extends into the back, shoulder, or arm. Deep breathing makes it worse. The patient is frequently a sufferer from headache "over the whole head." The appetite is poor. The bowels have been very constipated. The patient has no cough and has not lost weight. He sweats at night occasionally; does not feel feverish or chilly. At times he has aching pains in the legs.

Status Præsens.—The patient is poorly nourished and of slender build. There is slight general enlargement of the lymph glands. The tongue is moderately coated. Slight but definite cyanosis of the lips, ears, and nail-beds is seen. Eyes negative.

Heart and lungs are negative throughout on inspection, percussion, and auscultation Pulse 75. Temperature normal.

Abdomen looks natural. The aorta is readily felt and tenderness is complained of on palpating it. The edge of the liver is just felt. With the patient on his back the spleen is palpable and descends about 1 cm. below the costal margin. Splenic dulness begins on the 8th rib in the middle axillary line, and extends almost to the border of the ribs.

Dermatographia was very active. Knee jerks active.

The patient was given cascara and instructed to return a week later for blood examination.

April 8, 1908. *Blood examination* showed: R. b. c. 4,925,000; w. b. c. 8,600; hb. 99% (Sahli). Smears of the blood stained with Hasting's stain showed nothing unusual, but unfortunately a differential count was not made. Spectroscopic examination of the blood for the bands of methæmoglobin and sulph-hæmoglobin was negative.

(Subsequent attempts to locate the patient have failed, so that further study of the case was impossible.)

The notes of these two cases show their close parallelism. In neither could a history of malaria or syphilis be obtained to account for the splenic tumor; splenic anæmia did not exist, nor was there any evidence of amyloid disease. The blood examination excluded a leukæmia, and there were no grounds on which to base a diagnosis of Hodgkin's disease. There was no valvular disease of the heart, no pulmonary emphysema, to account for the cyanosis. Sulph-hæmoglobinæmia and methæmoglobinæmia, of which thirteen cases have been collected by West and Clarke (1) up to 1907, and another added by Russell and Leathes (2), were thought of as possible explanations of the cyanosis. The latter is not uncommon in these cases, but differs, according to Osler (3), in that it resembles more the ashen hue of argyria, as contrasted with the plethoric cyanosis of erythræmia. Splenic

tumor, which does not appear in the summary of West and Clarke, was found in both of my patients. Furthermore, repeated spectroscopic examinations of the blood in one case and a single examination in the other revealed only the bands of oxyhæmoglobin, even in concentrated solution, thus excluding sulph-hæmoglobinæmia and methæmoglobinæmia. Tuberculosis of the spleen, associated with splenic tumor, cyanosis, and polycythæmia, has been reported by Rendu and Widal (4) and by Moutard-Martin and Lefas (5); subsequent autopsies on cases of polycythæmia with splenomegaly have not shown a similar lesion. This possibility, though rare, must be kept in mind. Such a condition cannot be definitely excluded in Case II, though it is extremely unlikely to have been present. With the negative tuberculin test in Case I, confirming the physical findings, as it does, it is reasonably certain that an active tuberculous process is not at the base of the patient's condition.

Were it not for the normal blood counts, both of the cases reported above would be characteristic examples of erythræmia,[1] of which Parkes Weber (6) has recently published an excellent critical review. He defines erythræmia as "a disease or morbid condition characterized by well-marked persistent relative and absolute polycythæmia (increase in the number of the red blood corpuscles) due to an excessive erythroblastic activity of the bone marrow, which appears to be the primary morbid factor in the condition; it is characterized likewise by persistent increase in the viscosity and total volume of the blood, and usually by a cyanotic appearance of the patient and by enlargement of the spleen." This definition coincides with the prevailing opinion of the disease. Autopsies have revealed a red, hyperplastic marrow in the shafts of the long bones, and the disease has been looked upon as analogous to leukæmia; hence the name, erythræmia, proposed by Türk.

From Dr. Weber's definition, it is evident that the *sine qua non* for a diagnosis during life is a persistent increase in the number of red cells in the blood. This has been found, almost constantly—though normal counts have been reported, generally coincident with a complicating (terminal) disease (sepsis, hæmorrhages)—in every case thus far recorded. Of the two remaining cardinal signs, cyanosis has been absent in some cases, while splenomegaly has been of more constant occurrence, according to Weber.

Microscopic examination of the stained blood in erythræmia has shown no constant abnormalities by which the disease can be recognized. Polychromatophilia is frequently seen. Nucleated reds are not uncommon, and are often present in considerable numbers. They have, however, been absent in some cases, even after prolonged search; but Boycott (7) expresses the belief that repeated examinations will reveal their presence in every case. From Naegeli's (8) careful analysis of the literature, it appears that myelocytes are of very frequent occurrence, and eosinophiles and mast cells are usually present in increased number. Myelocytosis is, as a rule, coincident with leukocytosis, but in one of Naegeli's patients the myelocytes amounted to one per cent with a total white count of only 6800. While we may encounter, then, pathological changes in the stained blood (polychromatophilia, normoblasts, megaloblasts (rare), myelocytes, eosinophilia, etc.), there are, nevertheless, no pathognomonic alterations, by which an absolute diagnosis of erythræmia can be made. The one characteristic blood feature thus far discovered is a polycythæmia with increase of viscosity. We are, therefore, not justified at present in making a positive diagnosis of erythræmia during life in the absence of an increase in the number of red cells.

In the history of leukæmia, there was a period, in which it was considered essential that there be a marked increase in the number of the white cells of the blood. As knowledge of the disease progressed and its morbid anatomy and hæmatology were more closely studied, cases of so-called aleukæmic leukæmia, *i. e.*, leukæmia with normal or subnormal white counts, were recognized. If the generally accepted theory of erythræmia be correct and we have in this disease the red cell analogue of leukæmia, it seems likely, to carry the analogy still further, that we will soon be able to recognize cases of erythræmia without increase in the number of red cells, or even with subnormal red counts. Were such a phase of the disease proven to exist, it would be designated properly "anerythræmic" erythræmia. That there is, or is not, an anerythræmic erythræmia may be demonstrated with our present knowledge (1) by clinical observation of cases, such as those recorded here, with a view to demonstrating a subsequent (or previous) polycythæmia, or (2) by the post mortem finding of the characteristic pathological changes in anerythræmic, but otherwise typical, examples of the disease.

In the cases reported above the suspicion has been strong that each represented an early (?) stage of erythræmia. The histories are quite suggestive—excepting the epilepsy in Case I, which could have no apparent bearing on a possible erythræmia—and physical examination demonstrated two of the three cardinal signs, *i. e.*, chronic cyanosis and splenomegaly. The usual causes of cyanosis and splenomegaly, excepting erythræmia, have been reasonably excluded, especially in Case I The repeated finding of myelocytes in the blood of Case I is an abnormality which I have been able to explain on no other ground than that of undue activity (hyperplasia) of the bone marrow, the essential anatomical alteration of erythræmia. The eosinophilia noted early in Case I has been interpreted similarly, since no other adequate cause for it could be found. Eosinophilia of like significance is not uncommon in pernicious anæmia, for example, presaging, as it often does, a period of improvement with marked regeneration (and consequent hyperplasia of the bone marrow). For the reasons just given and by the process of exclusion, the provisional diagnosis of anerythræmic erythræmia has been made; for it seems improbable that the patients have been the subjects of a new, hitherto unrecognized clinical entity.

[1] Synonyms: Splenomegalic polycythæmia; myelopathic polycythæmia; polycythæmia with chronic cyanosis; erythrocytosis megalosplenica; Vaquez's disease; Osler's disease.

If the narration of these cases aids in any way in proving or disproving the existence of an anerythræmic stage in erythræmia, the object of the report will be attained.

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ON THE EXCRETION OF CREATININ IN THE INFANT WITH SOME NOTES REGARDING ITS OCCURRENCE IN AMNIOTIC FLUID.

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Until recently the opinion was held that the urine of infants did not contain any creatinin or that the creatinin did not occur constantly. It has been shown that this opinion was erroneous and that creatinin forms a regular constituent of the infant's urine. Moreover the amounts present, though smaller in proportion to the body-weight than in the adult, do not show much greater individual variations than are observed in the adult. The following table reproduces the result of the investigations obtained on infants which did not show any signs of ill health.

Table I.

Name of authors.	No.	Age of infants.	Weight in gm.	Total (24 hrs.) creatinin in mg.	Creatinin in mg. per kg.	Creatinin coefficient (Shaffer).
Amberg and Morril.	I.	10 days.	4033	26.82	6.71	2.5
	II.	10 days.	3463	26.92	7.78	2.9
	III.	14 days.	2723	27.05	9.94	3.7
	IV.	7 days.	3093	17.48	5.46	2.1
	V.	13 days.	3100	30.1	9.7	3.6
(avg. of 6 days)	VI.	1 mo.	4561	35.3	7.4	2.9
Funaro.	VII.	1½ mos.	3500	17.5	5.0	1.9
	VIII.	2 mos.	4000	21.0	5.25	1.95
	IX.	2½ mos.	4300	28.0	6.51	2.4
	X.	3 mos.	4380	31.2	7.12	2.6
	XI.	3 mos.	4000	30.4	7.6	2.8
	XII.	3 mos.	4800	42.0	8.75	3.3

With exception of No. XII all the infants were breast-fed.

The age of the infants in this table varies between seven days and three months. It seemed desirable to extend the investigation to the first days of life and the results are recorded in Table II.

Table II.

No.	Weight.	Total (24 hrs.) creatinin in mg.	Creatinin per kg. in mg.	Creatinin coefficient (Shaffer).
A.	4.95	20.65	4.2	1.56
B.	3.12	5.65	1.8	0.67
C.	3.72	6.48	1.7	0.65
D.	4.2	17.35	4.2	1.53
E.	4.3	8.5	2.0	0.73

In all these cases [1] the urine of the first 48 hours was collected under the necessary precautions. The reaction of the urine was always acid to litmus. The urine did not reduce Fehling's solution, but contained more or less albumin. The amounts of urine and the specific gravity were as follows:

	Urine of 48 hours in cc.	Specific gravity.
A	193	1005
B	27	1010
C	59	1003
D	58	1010
E	23	1008

The following short abstracts from the histories may illustrate the general condition of the infants:

Case A.—C., white (obstetrical No. 3831), weighed at birth 5190 gm. and on the third day its weight fell to 4720 gm., the lowest point reached. On the thirteenth day it surpassed its birth-weight, being discharged on the eighteenth weighing 5350 gm. Its length at birth was 55 cm.; it was born of a multipara. Its temperature and bowel movements were normal. It received the breast every three hours and from the second day some additional feeding of cow's milk.

Case B.—B., colored (obstetrical No. 3853), weighed at birth 3270, on the second day 3125 and on third 3070 gm. From this lowest weight it surpassed the birth-weight on the seventh and left on the fourteenth day, with a weight of 3600 gm. Its length at birth was 51.5 cm.; and it was a first-born child. Its temperature varied on the first day between 96.2° and 98.6° F.; on the second between 96.2° and 98.6° F. From the fourth to the seventh day the temperature did not reach 96° F. On the fourth day a jaundice was noted. The bowel movements were normal. The baby received the breast at three-hour intervals.

Case C.—C., colored (obstetrical No. 3912), weighed at birth 3850, on the second day 3710 and on third 3590 gm. From this lowest level the birth-weight was nearly regained on the fifth day. The baby left on the fourteenth day with a weight of 4145 gm. Its length at birth was 49.5 cm.; it was born of a multipara. On the fourth day the temperature became normal and remained so; previously it had been subnormal. The bowel movements were normal. The baby was put to the breast every three hours.

[1] The difficulty of collecting the urine of infants quantitatively without having a trustworthy person to watch its collection, made it impossible to examine a larger number of cases. That we were able to obtain the urine of our cases, we owe to the courtesy of Miss C. Turford, head nurse of the obstetrical ward of the Johns Hopkins Hospital, and we wish to acknowledge our indebtedness to her kindness. Our thanks are due, to not a small degree, to the interest and help which Dr. H. J. Storrs, resident obstetrician at the Johns Hopkins Hospital, has extended to us.

CASE D.—J., white (obstetrical No. 3943), weighed at birth 4350, on the second day 4180, and on the third 4020 gm. The lowest level of 4010 gm. was reached on the fourth day. The baby left on the fourteenth day without having regained its birth-weight. The weight was then 4300 gm. Its length at birth was 54 cm.; it was born of a multipara. The temperature reached normal on the fourth day. The bowel movements were normal. It received the breast every three hours.

CASE E.—M., white (obstetrical No. 3943), weighed at birth 4430, on the second day 4340, and on the third 4220 gm. The lowest level was reached on fourth day with 4200 gm. and it left on the fourteenth weighing 4409 gm., not having regained the birth-weight. Its length at birth was 56 cm.; it was born of a multipara. The temperature was normal, and also the bowel movements. The breast was given every three hours.

For several reasons some of the creatinin determinations are not absolutely exact. It is necessary to remove the albumin and with a few portions of urine this was accomplished by treating the urine with basic lead acetate. The lead is removed in the usual manner with H_2S; the filtrate from the lead precipitate is evaporated to dryness, and the residue is taken up in water and then filtered. Preliminary experiments showed that a small loss of creatinin occurs in this manner.

In order to avoid this loss it was deemed advisable to proceed as follows, boil the urine with a few drops of acetic acid and according to the specific gravity of the urine the filtrate was either used directly or after concentration. Care must be taken that the readings with the Duboscq calorimeter fall within the prescribed limits (1). For instance in Case A the reading for the part of urine treated with lead acetate was 4.35 and for the part boiled with acetic acid filtered and evaporated it was 4, while it should fall between 5 and 13. Under such circumstances the creatinin determination will result in figures which are too low.

The same example shows the loss due to the treatment with lead acetate. The total amount of creatinin was 41.3 mg. when the urine was not treated with lead acetate, and when this salt had been added it was 38 mg.

A further source of error in the lead-acetate method may be introduced in the evaporation of the voluminous filtrate from the lead precipitate. This is naturally rather strongly acid and the long heating may convert some creatin, if any is present, to creatinin, Mellanby (2) and Rothmann (3). In our preliminary experiments this source of error did not occur because the urine used did not contain any creatin. Former experiments have shown that under usual conditions the evaporation of the natural acid urine did not give rise to this error. In all cases determinations were made with urine not treated with lead acetate and in Cases D and E without evaporating the urine.

Comparing the results of Tables I and II it seems that the creatinin excretion during the first two days of life is smaller than later on. Naturally a larger series of cases will have to be examined before this can be accepted as a general rule and it will be necessary to follow the excretion in the same individual for some time.

The question arises whether the creatinin excreted by the infant during the first days could derive its origin from the amniotic fluid or the mother's blood. We were able to examine the amniotic fluid in two cases. In a case of hydramnion 1160 cc., and in a normal case 585 cc. of amniotic fluid were collected; its reaction was neutral to litmus.

After treatment with basic lead acetate the amount of creatinin in the 1160 cc. of amniotic fluid was found to be 16.8 mg. and when determined with the filtrate after boiling with acetic acid 17.9 mg. The total amount of creatinin in the 585 cc. of fluid was found to be 9.3 mg., after treatment with lead acetate. It is of interest to note that in these two cases the amount of creatinin in milligrams per 100 cc. fluid was nearly the same, in the case of the hydramnion 1.5 and in the other 1.6 mg. The possibility has to be considered, that the creatinin enters the amniotic fluid as a urinary constituent of the fœtus. But the preponderance of opinion seems to favor the view that the amniotic fluid is derived from the maternal blood serum, which has been altered by some specific activity on the part of the amniotic epithelium, Goenner (4), Williams (5). Whether or not the creatinin content of the amniotic fluid can be used as an indication that a urinary excretion of the fœtus enters into its composition, is a question which we will have to leave open.

The urine of Case D was collected again on the fifth and sixth days, and it contained 18.3 mg. creatinin for twenty-four hours, with 4.4 mg. per kilogram and a creatinin coefficient of 1.65; that is, the values obtained differed only very slightly from those of the first forty-eight hours. This result makes it rather improbable that the creatinin excreted during the first forty-eight hours should derive its origin to any extent from the amniotic fluid or the mother's blood.

With regard to the creatin, the urine of Case E only could be examined and none was found. In two cases previously reported a small amount of creatin was found and in the second case it was found in each of the six periods of forty-eight hours, only being absent or not present in determinable amounts during a period of water diet.

To complete the data collected thus far concerning the excretion of creatinin in infants the further results of Funaro (6) may be cited first in the following table:

TABLE III.

No.	Age.	Weight in gm.	Diagnosis.	Diet.	Total (24 hrs.) creatinin in mg.	Creatinin per kg. in mg.	Creatinin coefficient (Shaffer).
1.	2 mos.	3000	Lues cong.	Hum. milk, buttermilk.	21.0	7.0	2.6
2.	3½ "	2500	Lues.	Hum. milk.	17.25	6.9	2.6
3.	4½ "	4000	Enteritis.	Hum. milk, buttermilk.	24.7	6.17	2.3
4.	5 "	3900	Enteritis.	Buttermilk.	24.5	6.28	2.3
5.	7 "	4775	Chronic disorder of nutrition.	Buttermilk.	52.0	10.91	4.0
6.	9 "	4000	Atrophy.	Buttermilk.	22.5? (5.5)	4.62??	2.1
7.	9 "	6500	Encephalitis.	⅔ milk.	24.0	3.7	1.4
8.	9 "	8300	Eczema.	⅔ milk.	60.0	7.23	2.7
9.	10 "	7200	Chronic disorder of nutrition.	Buttermilk.	37.95	5.27	2.0

Besides Funaro determined in three of his cases the creatinin output on different days and with different diets

		Diet.	Creatinin per 24 hrs. in mg.	
Table III.	8	⅔ milk.	60.0	Funaro.
		⅔ milk.	55.0	
		⅓ milk.	77.0	
		⅓ milk with casein and fat.	67.2	
		⅓ milk.	60.0	
Table III.	6	Buttermilk.	75.0	
		⅔ milk.	65.0	
		Buttermilk.	63.0	
Table I.	12	⅓ milk.	42.0	
		⅓ milk sugar.	40.0	
		⅓ milk with casein butter.	36.0	
		Casein and fat.	38.0	
Table I.	6	Human milk.	38.5	Amberg and Morril (7).
		Do.	29.6 (?)	
		Do.	37.6	
		Modified human milk.	33.2	
		Do.	29.9	
		Do.	31.4	

With regard to the creatinin nitrogen expressed in per cent of the total nitrogen of the infant's urine the following data are at our disposal. In the five cases reported by Amberg and Morril (8) concerning normal breast-fed infants between the ages of 7 and 13 days the creatinin nitrogen participated in the total nitrogen with 2.56, 3.6, 3.61, 2.98, and 2.72%. While the creatinin excretion per kilogram in the infant falls below that of the adult, the creatinin nitrogen participates in the total nitrogen output in the urine to the same extent as in the adult on a diet rich in protein.

In the other case reported by the same authors concerning a normal breast-fed infant about one month old, these figures were for the first three periods 2.2, 2.0, 2.4% and when the diet was modified to approach an "Erhaltungsdiät" they rose to 3.0, 4.3 and 4.5%. It will be of advantage to inquire whether the data thus far collected about the excretion of creatinin in the infant permit us to draw some conclusions particularly with reference to their possible clinical applications. This question leads us by necessity to a short consideration of the theories which have been advanced about the significance of the creatinin excretion. Folin (9) sees in the creatinin excretion an indicator of the endogenous nitrogen metabolism and makes it depedent on the active mass of protoplasm. At the same time he claims an entire independence between the creatin and creatinin in the economy of the organism. Shaffer (10) modified this view. The creatinin excretion is an index of some special process of normal metabolism taking place largely, if not wholly, in the muscles. Upon the intensity of this process appears to depend the muscular efficiency of the individual. He introduces his creatinin coefficient,[2] which expresses the amount of creatinin nitrogen in milligrams per kilo of body-weight in twenty-four hours. In strictly normal adults this creatinin coefficient varies between 7 and 11 mg. In pathological subjects this coefficient is usually low. The excretion of creatin on a diet free from it is referable to a rapid loss of muscle protein. Mellanby (l. c.) claims that the liver produces creatinin which in the developing muscle is transformed to creatin, and only makes its appearance in the urine when the muscle is saturated with creatin. With a loss of liver activity in pathological cases he found a diminution of the creatinin excretion. The muscles play a small part in the formation of creatinin. Folin's view concerning the entire independence of creatin and creatinin in the economy has lost in probability particularly through the experiments of Gottlieb and Stangassinger (11) (confirmed by van Hoogenhuyze and Verploegh (12) and Rothmann (3)). These authors demonstrated the presence of ferments in tissues capable of transforming creatin to creatinin, besides others capable of destroying either one. Van Hoogenhuyze and Verploegh assume that creatin is formed in different organs as a product of metabolism, and particularly in the liver. The circulating blood removes the creatin from the organs. A great part is further oxidized, another part is converted to creatinin. The same authors consider their results as a further confirmation of the hypothesis of Folin that a stimulation of the life process of the cells of the body expresses itself in an increased creatinin excretion. The small amounts of creatinin excreted a short time after birth are said not to contradict this view.

It is not proved that during this period of life the organism should not utilize to a much greater extent than later the chemical energy of the creatin formed in the body. In the infant the building up of new cells exceeds by far their destruction and therefore it is not improbable that an intermediary metabolic product like creatin is much better utilized than in the adult.

With regard to the theory advanced by Mellanby (l. c.) we should like to point out an interesting fact. Mellanby deduced from his experiments on the chick that the creatin content of the muscle is dependent on the growth of the liver. At a time when this organ enlarges rapidly the creatin content of the muscles increases rapidly, although the muscular growth almost stops. Creatinin is not excreted by chickens until about a week after hatching, *i. e.,* not until the muscles are saturated with creatin. All the data at our command show that the creatinin excretion of infants is certainly much smaller than in the adult. At the same time the liver is certainly larger in proportion to the body-weight during infancy than in adult life; the proportions given by Harley (13) (see Czerny and Keller) are in the new-born 1 : 18, in infants 1 : 20 and in the adult 1 : 50. The muscles of the new-born infant on the other side constitute only 23% of the body-weight, while those of an adult constitute 43% of the total weight (14). According to Mellanby's hypothesis one would

[2] In the tables we have given the creatinin coefficient of Shaffer. This coefficient is readily determined by multiplying the amount of creatinin excreted per kilogram by 0.372. Since this factor is a constant the coefficient varies directly with the amount of creatinin per kilogram and therefore it does not seem to offer any particular advantages over the calculation of the creatinin in milligrams per kilogram in twenty-four hours. It may be better to reserve the term creatinin coefficient to express the creatinin nitrogen in per cent of the total nitrogen similarly to the way in which the term ammonia coefficient is used.

predict *a priori* that this relatively large liver would rapidly produce sufficient creatinin to quickly saturate the small amount of muscle tissue with creatin and that subsequently there would be a relatively greater excretion of creatinin in the urine of the infant. This, however, is certainly not the case.

The paper of Mendel (15) on the physiological significance of creatin and creatinin furnishes a critical review of the hypotheses advanced by the different authors. From this exposé we learn that this problem is of a rather complicated nature and needs further elucidation. Therefore we will abstain from entering into a more detailed discussion, particularly with regard to the results thus far obtained in pathological cases, heeding the author's warning, "Clinical investigators seem to forget that in these experiments of nature one rarely deals with simple conditions where a single organ, such as liver or muscle, is independently involved."

Nevertheless, while the single steps by which the end result is reached need further elucidation, it seems to us that a few conclusions may be reached from the end result. Thus the work of Folin and others (van Hoogenhuyze and Verploegh, Klercker (16)) seems to establish rather firmly that the creatinin excretion may really serve as an indicator of the endogenous nitrogen metabolism; and furthermore, at present at least, the work of Shaffer (l. c.) makes the idea of a close connection between some process in the muscles and the creatinin excretion rather attractive. The relatively small creatinin output in the normal infant certainly could find its explanation to a large extent on this latter assumption as has been pointed out before. And the result obtained from the study of the nitrogen partition in the urine of baby Davis (Amberg and Morril) could again be explained on Folin's and particularly Shaffer's theory. In this case the creatinin nitrogen formed on an average 2.2% of the total nitrogen on regular breast feeding. On a diet consisting of human milk modified in such a manner that it approached an "Erhaltungsdiät" the creatinin nitrogen formed on an average 3.9% of the total nitrogen, rising to 4.5% on the lowest protein diet.

This relative increase of the creatinin nitrogen was not as high as that observed by Folin on his diet poor in protein. According to the theory of Shaffer this result should have been expected, since the muscles of the infant form a smaller percentage of the body-weight than in the adult. Under such conditions, therefore, it could hardly be expected that the products of the muscle metabolism participate to the same extent in the products of the endogenous metabolism as in the adult. We have referred repeatedly to the relatively small amount of creatinin per kilogram excreted by the normal infant, when compared to that excreted by the adult. Amberg and Morril were the first to show this condition on the basis of quantitative determinations with the 24-hour urine. These results were confirmed by Funaro, who, however, forgot to mention that two of the three conclusions he advances had been reached by these authors. His third conclusion based on the cases given above is that the individual variations under normal and pathological conditions are not very great and that also when the diet of the individual is changed. It must be conceded, however, that the variations observed in different individuals are not very inconsiderable, but neither an influence of the age nor of the diet nor of the condition of the infant can be made out definitely from the data given. Since the diet of the infant may be considered as practically free from creatin or creatinin, an influence on the creatinin excretion could not well be expected.

An influence of the age must exist due to the gradual changes of the organism to the adult state, but it may be easily understood that this influence will show itself strikingly only when longer periods of time are taken in consideration. Rather remarkable is the fact that the condition of the infant, which may be judged to a certain extent by the weight, should not have shown a more definite influence. Number 6 of Table III, a case of atrophy with a weight of 4 kg. at an age of 9 months, excreted 4.62 mg. creatinin per kilogram and had a creatinin coefficient of 2.1 mg. A mistake must have occurred, since according to the figures given by Funaro the creatinin excreted in milligrams per kilogram should read 5.5. A further discrepancy is noted; it seems that in the same case the creatinin excretion was followed on different days on different diets and its amount is given as 75, 65 and 63 mg. in twenty-four hours, while in the table it is given as 22.5 mg. These mistakes are the more unfortunate as a study of just such cases would be of particular interest. For it has been shown that a number of ferment activities of different organs has suffered severely in the atrophic infants.

The results of the investigations on infants to which we have alluded in this paper are not very numerous, and a rather limited number of pathological cases have been recorded and the information concerning these pathological cases is rather scanty. But it does not appear very promising that the creatinin determination should furnish us much additional clinical information of greater value. The possibility cannot be denied that in cases of malignant tumors the creatinin determinations may be of some value; and a further study, particularly of severer disorders of nutrition, is very desirable, and it is not precluded that the creatinin and creatin excretion may be of some prognostic value in such cases.

The results obtained in the first forty-eight hours are certainly rather remarkable, giving the lowest figures for the creatinin excretion as yet observed in infants. At present we must content ourselves with stating our results, leaving any effort at explanation to a larger number of observations and particularly to observations following the creatinin and creatin excretion for some time in the same individual.

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A METHOD OF SPLINTING SKIN GRAFTS.

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Every surgeon has his own pet method of dressing skin grafts, and fairly good results are obtained when the grafted wound is dressed with gauze moistened with normal salt, or borax solution, 1:40; with overlapping strips of rubber protective; with dry gauze or powders; with silver foil; or when it is simply left exposed to the air without any dressing. However, there are many partial takes and failures for the reason that the grafts are not properly splinted after they are applied, and in consequence slip down with the dressings, or are floated off by blood or serum collecting beneath them. In order to overcome this difficulty it is necessary to reinforce the grafts with some material which has enough body to act as a splint, and at the same time is not too rigid to shape itself readily to any desired location. It is also very important that it should not adhere to the grafts and granulations, or cause too much pressure, and that there be free escape of any secretions into the dressings.

After experimenting with various materials, I tried a coarse meshed net, such as is used for curtains. It is made of loosely woven flat bars of cotton thread, surrounding openings about 1 cm. in diameter. It is necessary to have the openings approximately this size as smaller ones often become clogged. This proved too flimsy, and also became adherent to the grafts. So in order to increase the body of the fabric, after washing out the sizing and drying, I soaked the material in a rubber solution made up of pure gutta-percha, from 15 to 30 parts (depending on the stiffness of material required), and chloroform 150 parts, and found that after the chloroform had evaporated and the material was dry there was enough stiffness to give a very satisfactory splinting material. When prepared the net should be of a light greyish-brown color throughout.

The Sterilization Before Application is as Follows.—Cut in pieces as large as may be desired and separate them with one or two thicknesses of gauze. Place in a sterile jar, and fill it with 1:1000 bichloride of mercury solution. Change this solution three times with twelve-hour intervals, and finally allow the mesh to remain permanently in 1:1000 bichloride solution. It can be kept for a considerable time in this way (I have used it after keeping it nine months in the bichloride solution), although it is better to make up small quantities and often. The dry permeated material will keep indefinitely. No hot solutions must come in contact with the mesh during the sterilization or application.

Technic.—After the grafts are in place the mesh is taken out of the bichloride solution and thoroughly rinsed with salt solution, then dried with a sterile towel. A piece is cut large enough to allow a margin around the grafted area of from 5 to 10 cm. Then the material is applied and pressed snugly down on the grafted area and surrounding skin or granulations. Should the conformation of the part or wound not permit the mesh to be evenly applied, a few cuts with scissors will allow an infolding and accurate fitting, which is necessary in order that the splinting may be successful. The overlapping edges may be secured to the skin by strips of adhesive plaster when necessary. After the net is in position the dressing selected is applied, and the whole secured by a bandage.

Where the overlapping material rests on granulation tissue, it will be found that it can be lifted up at any time without causing pain or bleeding, as the granulations do not adhere to or grow into the bars of the impregnated material.

With this mesh in place the grafts can be observed from time to time with little or no danger of displacing them. The first dressing is usually made 36 to 72 hours after operation, and if the gauze next to the mesh has dried out, it must be thoroughly soaked with salt solution, and then carefully lifted with an instrument, while with a pledget of gauze the net is held down, as the dressing is raised from it, in order to guard against any displacement. Then the wound is irrigated with salt solution, and any secretions wiped away. The mesh is left in place from 4 to 10 days, and then can be removed without any difficulty.

Any type of dressing may be used over this material—silver foil, wet or dry gauze, etc., and I have found it particularly desirable in those cases where the grafted area was exposed to the air.

Conclusions.—The use of such a material permeated with

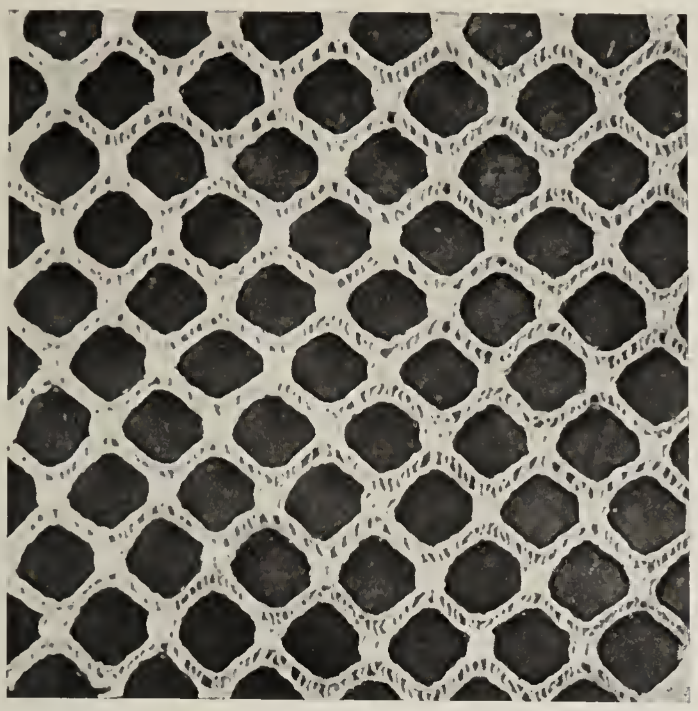


Fig. 1.—The actual size of the openings of the mesh.

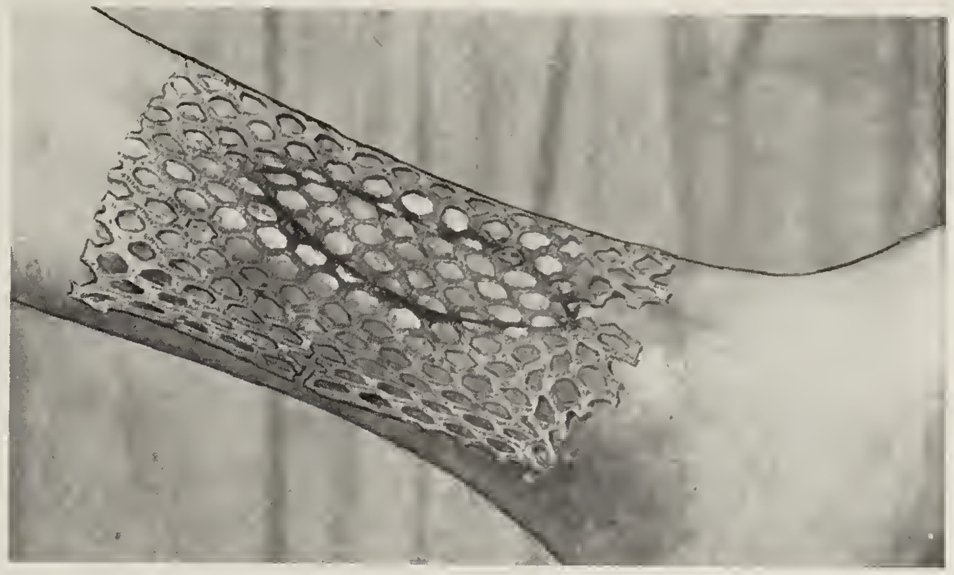


Fig. 2.—The material splinting a whole thickness graft on ulcer following osteomyelitis of tibia. Note cuts to allow accurate fitting. Photograph taken four days after application of mesh.

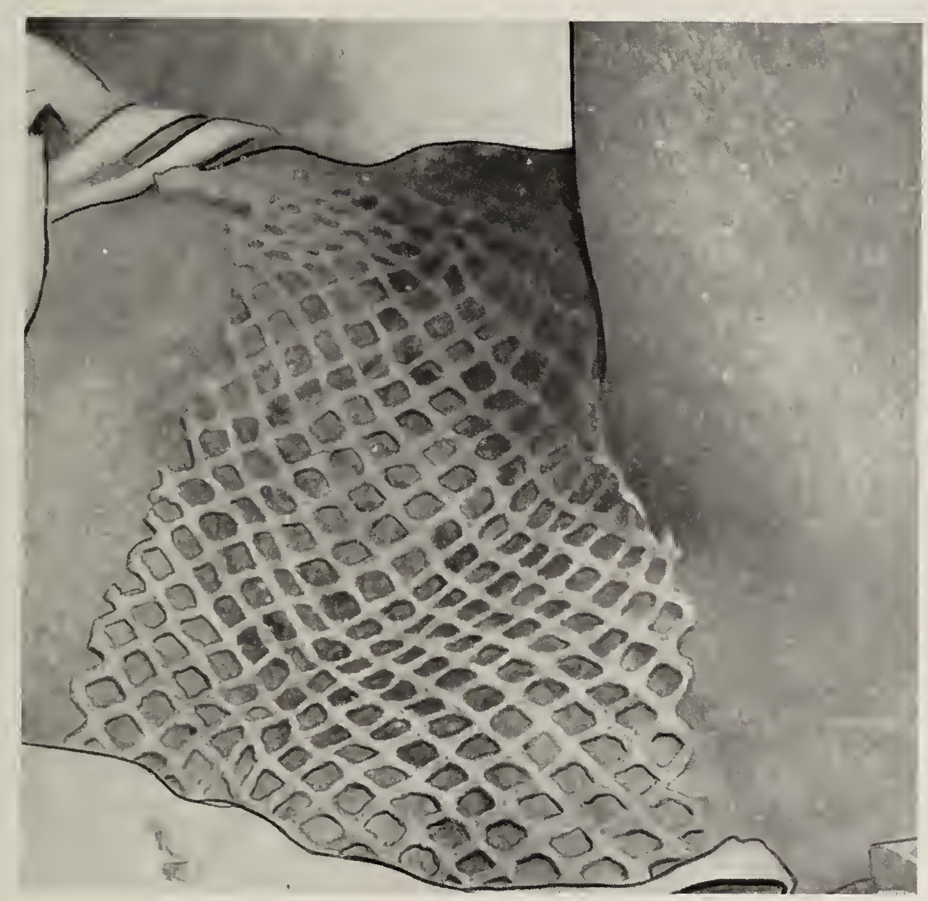


Fig. 3.—Illustrates the close fitting of the mesh over a Thiersch graft on deep breast wound following excision of carcinoma on a very fat woman.

Fig. 5.—Mesh over partial whole thickness graft on ulcer of thigh. Photograph taken four days after application.

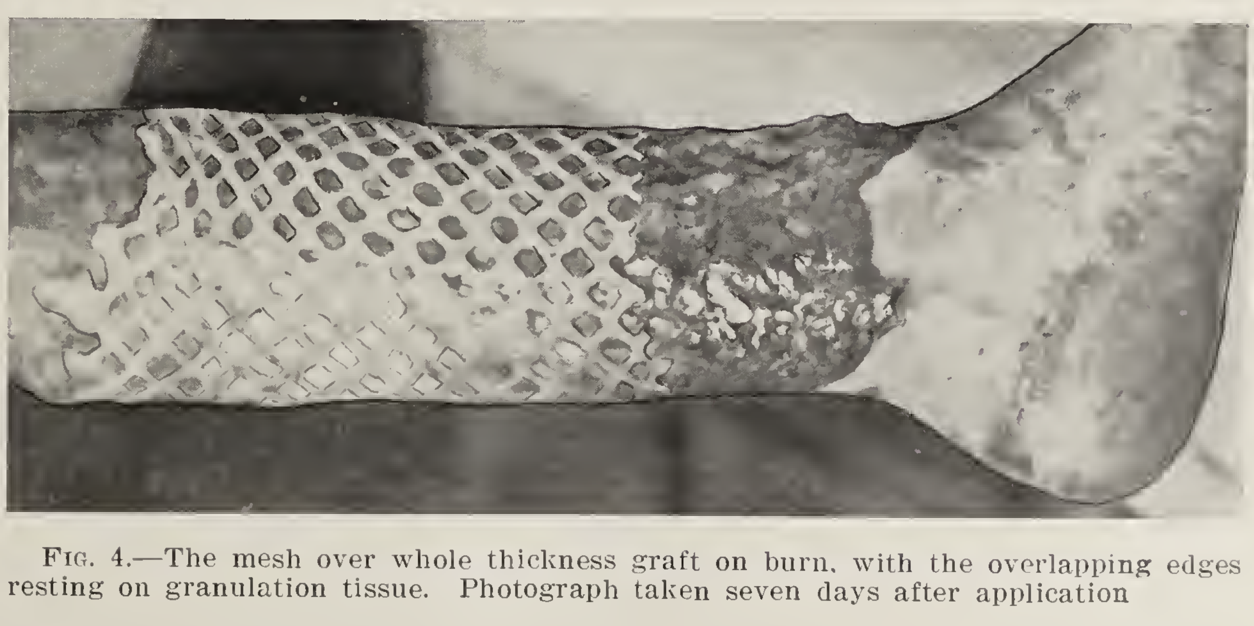


Fig. 4.—The mesh over whole thickness graft on burn, with the overlapping edges resting on granulation tissue. Photograph taken seven days after application

rubber is advantageous in that it splints the grafts without too much pressure, and is easy to apply and secure in place. It does not adhere to the grafts or granulations. It allows the free escape of any secretions which may form, and thus prevents maceration. Any sort of dressing may be placed over it. The progress of the healing may be observed at any time without danger of displacing the grafts. Should blisters form and serum or blood collect beneath the grafts, it can be removed at once.

I have used this open-mesh material over Thiersch and whole thickness grafts, on nearly every part of the body, and have found its use a distinct advantage.

Note.—This paper appeared in the Annals of Surgery, March, 1909.

A PRACTICAL METHOD OF IMITATING THE NORMAL AND ABNORMAL HEART SOUNDS FOR TEACHING.[1]

By Charles W. Larned, M.D.,
Instructor in Medicine, Johns Hopkins University.

Dissatisfaction with the methods commonly employed in teaching the heart sounds, normal as well as abnormal, led me some years ago into the field of experimentation, my object being to produce, outside the body, tones which when conveyed to the ear would represent with a reasonable degree of exactness, at least in force and rhythm, the sounds heard through the stethescope placed upon the patient's chest.

Of the several methods studied I shall mention only four and describe in detail only one. In all instances the sounds are produced by taps, strokes and what I shall term tap-strokes and stroke-taps upon the conductor employed.

Method I. The left forearm is used as the conductor, the left hand being closely applied over the left ear, the taps and strokes being made upon the elbow.

Method II. The same, except that the taps and strokes are made not upon the elbow but upon the dorsum of the hand.

Method III. The stethescope is used as the conductor, the palm of the left hand being placed over the bell and the taps and strokes made upon the dorsum of the hand.

Method IV. The stethescope is used as the conductor and is applied to the right side of the bared chest, the taps and strokes being made upon the chest at a distance of some 2 to 4 inches from the bell. Distant and faint sounds can be produced by tapping over the pectoral muscles or in the intercostal spaces; loud and accentuated sounds by tapping over the ribs. The application of talcum powder to the surface stroked will soften the murmurs.

I shall now discuss briefly the merits and demerits of these several methods.

Methods I and II.—For over three years in my teaching I have employed the forearm as a conductor and I believe for normal heart sounds, for reduplications, and for normal and abnormal rhythm, this method gives the most realistic tones. A few weeks ago while demonstrating this method to my colleague, Dr. Henry Lee Smith, he suggested that the taps and strokes might be made equally well upon the dorsum of the left hand, and repeated trials have shown that certain abnormalities could be better imitated by following out this idea.

Methods III and IV.—Method III was given a trial but was soon discarded in view of the fact that the sounds conveyed are far too harsh. Method IV satisfies all reasonable requirements and I think is worthy of general employment. It has several advantages over the other methods, namely; the sounds produced are more realistic, the students become more rapidly familiar with the stethescope, and several students can be instructed at the same time. The great disadvantage in this method is that we must have a patient at all times for demonstration. I shall, therefore, in my detailed description deal with Method II, which can be employed without a subject, besides which this is the method best suited to those not familiar with the manipulations for producing the taps and strokes.

Position I.

To perfect oneself in the use of this method one requires but little practice, the only really troublesome sound to imitate being the presystolic rumble of mitral stenosis and even here the majority will have but little difficulty, a pianist should have none.

When practising upon oneself there are several positions that may be taken, but the two which give the best approximation for the ear hand and the freest manipulations for the percussing hand are as follows:

Position I. Turn the face well to the right and with the

[1] This paper was read before The Johns Hopkins Hospital Medical Society, December 20, 1909.

left forearm well back of the head place the hand closely about the ear.

Position II. Turn the face well to the left, place the left hand to the left ear, the forearm of the percussing hand being placed back of the head. The two photographs illustrate the two positions, in both of which the left hand acts as the conductor, the right hand as the plexor.

Definitions of the terms tap, stroke, tap-stroke and stroke-tap are as follows:

By *tap* I mean gentle percussion with the index or middle finger without movement of the forearm and with little, if any, at the wrist, the position of the finger being the same as in ordinary percussion, namely, flexed so that the terminal phalanx strikes the ear hand perpendicularly (otherwise the note produced is more or less impure), the strength and length of the tap depending upon the strength and duration of the note desired.

By *stroke* I mean the gentle drawing of the tip of the finger over the dorsum of the ear hand, a short stroke for

Position II.

short murmurs, a long stroke for long murmurs, the intensity of the murmur being indicated by the force of the stroke.

By *tap-stroke* I mean the direct merging of a tap into a stroke without any interval of time. It is made by ending the tap with a stroke before lifting the finger.

By *stroke-tap* I mean the direct merging of a stroke into a tap without any interval of time. This can only be done by the use of two fingers, the tap occurring simultaneously with the elevation of the stroking finger.

In demonstrating the method to a student it is well to have him place the right hand over the right ear with the elbow as far to the left as possible, and the face to the right. The instructor standing behind and slightly to the right makes upon the dorsum of hand so placed the taps, strokes, etc., which the condition he wishes to demonstrate may call for. A third photograph illustrates this position.

To obtain the best results the following points should be observed: The skin upon the dorsum of the hand should be smooth and not chapped, as a rough skin roughens the murmurs. A plump hand gives better imitations than a bony hand.

Accentuated sounds are best made by tapping directly over one of the metacarpal bones or over a knuckle; distant sounds are imitated by tapping over the muscles between the thumb and index finger.

Below are given as an example of what can be accomplished, the taps, strokes, tap-strokes and stroke-taps necessary to bring out the normal and abnormal sounds in some of the heart lesions most frequently met with. In each instance a diagrammatic representation is obtained by using certain symbols which with their equivalents are given below:

= tap } The force is indicated by the shading, the
= stroke } duration by the length.

= tap-stroke } The force and duration are indicated respectively by the shading and length of each
= stroke-tap } component part.

Vertical lines indicate the beginning of systole; the lettering shows the fingers used in the manipulation.

Position III.

The normal heart sounds as heard at the apex.—A light but rather long tap for the first sound followed by a lighter and shorter tap for the second sound, care being taken to observe the proper interval between the first and second sound, and the second and first sound.

Mitral insufficiency as heard at the apex—the murmur following and not replacing the first sound.—A tap-stroke made with the index finger to indicate the first sound and murmur followed by a light tap with the middle finger to indicate the normal second sound.

Aortic insufficiency as heard at the base, the murmur replacing the second sound.—A light tap made with the index

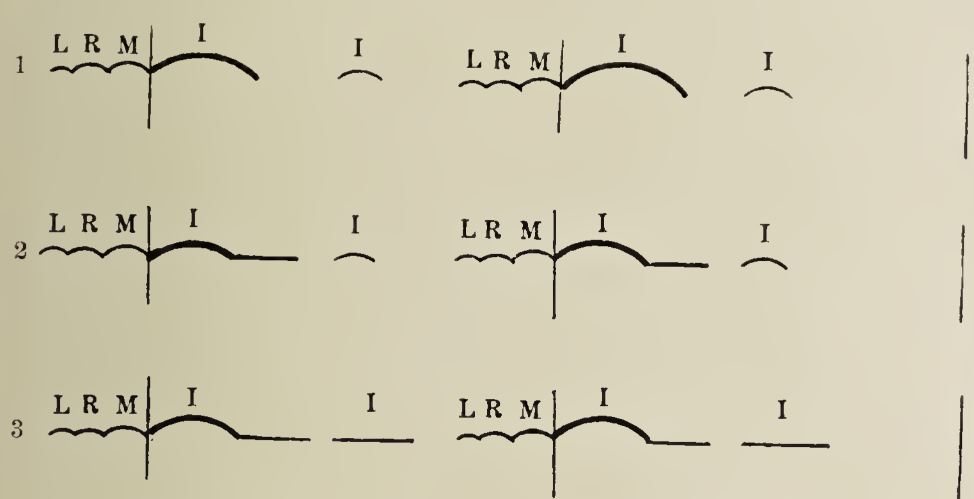
finger to indicate the first sound, followed by a stroke with the middle finger to indicate the diastolic murmur.

(1) *Mitral stenosis; (2) Mitral stenosis and insufficiency; (3) Mitral stenosis and insufficiency and aortic insufficiency; all as heard at the mitral area.*

(1) A rapid succession of four crescendo taps beginning with the little finger and ending with the index finger, the last tap being sufficiently strong to indicate the shock of the first sound, and immediately followed by a light tap to indicate the second sound.

(2) To bring out a systolic associated with the presystolic murmur convert the culminating tap of the presystolic rumble into a culminating tap-stroke, the stroke being lateral toward the little finger, light and short.

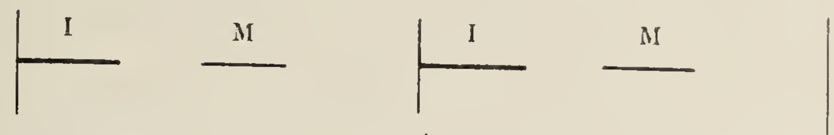
(3) To bring out a diastolic murmur associated with the presystolic or the presystolic and systolic make, instead of the



tap which represents the second sound, a short gentle stroke provided the murmur replaces the second sound, otherwise a tap-stroke, the stroke in either instance being lateral, toward the thumb, these two lateral strokes one for the systolic, the other for the diastolic murmur are best produced by a rocking motion at the wrist first to the ulnar then to the radial side.

Aortic stenosis as heard at the base.—A firm long scratching stroke made with the nail of the index finger to indicate the harsh systolic murmur, followed by a very gentle tap with the middle finger to indicate the relatively faint second sound.

Mitral and aortic insufficiency as heard at the apex, both sounds being replaced by murmurs.—A relatively long stroke with the index finger to indicate the systolic murmur, followed by a shorter and lighter stroke to indicate the diastolic murmur.



The pistol-shot sound heard over the arteries of the extremities in aortic insufficiency can be well imitated by a short sharp tap over the knuckle of the metacarpophalangeal joint of the middle or index finger.

Gallop rhythm, pendulum rhythm, reduplications, splitting of the first and second sounds and a variety of other conditions can all be well imitated.

In conclusion, I should like to state that I do not pretend to imply that by this method the sounds of the heart either in health or disease can be exactly reproduced, but what I do believe is, that the imitation of the rhythm, together with the time of occurrence of the normal as well as abnormal sounds, is sufficiently realistic to be most helpful to all teachers of physical diagnosis.

I wish before closing to express my thanks to Dr. Henry Lee Smith for having suggested the hand as a sound conductor, and also to give him credit for the imitation of the presystolic rumble which he so ingeniously worked out.

PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS MEDICAL SOCIETY.

October 18, 1909.

Dr. Frank R. Smith, the president, in the chair.

The first business of the meeting was the election of officers for the ensuing year, and Dr. Louis V. Hamman was duly elected president, and Dr. William L. Moss, secretary.

I. Demonstration of Tuberculides. Dr. C. von Pirquet.

The case which I will demonstrate this evening, a boy three years of age, shows a symptom of cutaneous tuberculosis which is not yet much known in America. I am sure that it will be found here as frequently as it is in Europe since we learned to make the diagnosis of this insignificant looking efflorescence. Tuberculosis of the skin in its serious aspects has been known for a long time, and we make the distinction principally of lupus and scrofuloderma. Among tuberculous skin diseases, tuberculide is the one not yet much known. Tuberculides comprise the following:

1. Lichen scrofulosorum.
2. Erythema induratum (Bazin).
3. Folliclis.

This last form has been first described by Barthelemy in 1891. In later years only the knowledge of it has spread to the German clinics. F. Hamburger has made a special study of its clinical aspects, and Leiner proved the presence of tubercle bacilli in these efflorescences, whereas formerly Hallopeau had thought they were due to toxines only. In this case you see both kinds of folliclis; a *papular necrotic* one is to be seen on the elbow. You find a hard papula about $\frac{1}{3}$ of an inch in size, covered with white crusts. It is a chronic dermatosis,

but generally disappears after some months or years, leaving scars. In this case the mother has noticed it since July.

The other form is to be seen on several points of the chest and back. It consists of very small papules, about 1/10 of an inch in diameter, of a livid red color. The characteristic points are: a lack of any tendency to ulcerate, then a depression in the center, and finally the fact that the papula has a little gloss on it (F. Hamburger). The mother could not say when the efflorescences first appeared, but as they are not of a very fresh color we can tell that they have been there for several weeks; new ones have a more reddish color. This form is called *papulosquamous*, because there is often a delicate scale on top of it, and only after the scale is taken off, the depression is seen in the center. All the forms of tuberculides are a definite sign of tuberculosis. They are seen not infrequently in children of the first year. They have certainly the meaning of an active spreading of tuberculosis, as tubercle bacilli have been found in them. It depends probably only on the number of tubercle bacilli put into the circulation, and of the parts of the body where the bacilli are scattered, whether this spreading will be a fatal one or will be overwhelmed by the organism. So we find a dense appearance of tuberculides often combined with miliary tuberculosis. It is an interesting fact that this form of tuberculides has been found, in several instances, appearing two or three weeks after measles, and I think it is due to the lack of tuberculous allergy which we find during that illness. In this case measles have not preceded. We do not see now any symptoms of a miliary spreading of tuberculous germs, but we have several proofs of the existence of tuberculosis. The abdomen is large and contains probably free fluid; the child has a chronic discharge from both ears. You can see a marked new cutaneous tuberculin reaction. The test was also made July last, and already was positive then.[1]

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II. A Report on Some Cases of Purpura Hæmorrhagica following Benzol Poisoning. Dr. L. Selling.

This paper will be published in the Bulletin.

Discussion.

Dr. T. R. Boggs.—Dr. Selling's observations have much interest from a practical standpoint. In the main they correspond with those reported by Dr. Bunting in his experiments on rabbits using saponin and ricin as the toxic agents.

Dr. W. S. Thayer.—It would be important to see if one could produce a chronic poisoning of the bone marrow with megaloblastic crises. I should like to ask Dr. Selling if he has observed any such crises in his experiments.

Dr. Selling (in reply to Dr. Thayer).—I have not. All the cells were of a normoblastic type.

Dr. H. A. Kelly.—Has any precaution been taken at the factory to prevent any repetition of the poisoning?

Dr. R. Norton.—Mr. Tolliver, the superintendent of the factory, has lent every possible aid in this investigation as to the possible cause for these cases of poisoning. The factory is well lighted and well ventilated, and these accidents seem to have been unavoidable. A substitute is now being used for benzol in the sealing of the cans.

III. A Review of the Surgical Anæsthesia given in the Surgical Clinic of The Johns Hopkins Hospital. Dr. W. D. Gatch.

This paper, together with further statistics, will be published in the Bulletin.

Discussion.

Dr. W. S. Thayer.—It just happened that I was present in the Massachusetts General Hospital at the time of their annual anniversary of the introduction of ether as an anæsthetic by Dr. Morton. On Ether Day, as the anniversary is called, a paper is read concerning the use of ether and its applications to the medical science. President Eliot read a most interesting paper on Animal Experimentation, emphasizing what a great part ether played in the advance of medical science. I was also fortunate in seeing Dr. Morton's original apparatus for the administration of ether. It consisted of a large glass bulb supported on an adjustable stand, and having at its top two apertures, one to receive a long wooden mouthpiece, through which the patient was to draw the ether gas. The second aperture in the bulb was to receive a sponge saturated with the ether.

Dr. H. A. Kelly.—I am glad Dr. Gatch has taken up this subject, and I hope he will include in his statistics those of the gynecological clinic of this hospital. To the best of my knowledge there has not been a single death attributable to the anæsthetic given in the gynecological service, or at my private sanitarium. We are not all so fortunate; only recently I witnessed the death of two patients on the operating tables of two very distinguished operators; in both cases the death could be attributed to the anæsthesia.

There is considerable danger in placing heavy, fat patients in the Trendelenburg position. The great weight of the intestines, and the heavy abdominal walls drag on the diaphragm and embarrass the heart's action. Twenty years ago I began using nitrous oxide as an anæsthetic, and I have never had cause to regret its use.

IV. On Paroxysmal Arteriospasm with Hypertension as an Accompaniment of the Gastric Crises of Tabes. Dr. L. F. Barker.

The patient shown was a white woman aged 49 years, a cigarmaker by occupation. Her complaint on admission to the hospital was severe pain in back and stomach with headache.

The family history was negative. The patient had been married twenty-four years; was the mother of six children, two of whom died in infancy. There is history of several miscarriages early in pregnancy.

Except for some vague rheumatic pains during the past ten years, she had suffered from no disease except the present illness.

Eight years ago the patient began to have pain in her back, indigestion, pain in the joints, especially shoulder and knees. Nausea occasionally accompanied the pain in the back. The attacks usually begin with the feeling of a lump in the throat, which the patient declares cannot be swallowed. Vomiting soon follows, and nothing can be retained upon her stomach. There is complaint of sensitiveness of the skin of the trunk. During the attacks there is no loss of consciousness, no disturbance of the sphincters; occasionally the patient has noticed palpitation of the heart. For the past year the attacks have averaged two per week, lasting from a few hours to three days. On examination, the patient was noted to be emaciated, the skin was sallow. Her eyes were rather prominent; there was a slight Von Graefe sign; the pupils were contracted and reacted but little to light and accommodation, but it was thought this might be due to the morphia, which she had been taking to relieve the pain. No glandular enlargement was found. The heart was slightly enlarged. The radials and temporals are tortuous and somewhat thickened. The lungs are negative, except for a moderate grade of emphysema.

An examination of the blood showed slight leucocytosis (13,800) and 92 per cent hæmoglobin. A differential count showed normal relations, except perhaps for slight increase of eosinophiles.

On October 13 the patient was observed by Dr. Barker, during a paroxysm of pain, and the following note was made: The face was very anxious, the lips cyanotic, eyes reddened and lachyrimose. One got the impression, at once, that the pain was that of organic disease. The radial pulse was 124, regular, but of high tension, feeling like a fine whipcord under the finger.

The blood pressure was measured at once and found to be about 190 mm. She was given an inhalation of amyl nitrite and the pressure fell at once to 90 mm. A short while after, however, the pressure again became high, rising to 200, and later to 210 mm. The knee jerks were over active, but the plantar reflexes were normal. The pupils did not respond to light. There was no tactile anæsthesia of the chest, but definite analgesia in large areas over the lower extremities. Nothing abnormal was made out on palpation of the abdomen. Examination of the urine revealed no albumin or casts.

A lumbar puncture was made by Dr. Kingsley and the spinal fluid found to be under pressure of 150-200 mm. The fluid was clear, colorless and contained 50 lymphocytes to the cubic millimeter. The serum-albumin test was positive.

Further sensory examination on October 15 showed both lower extremities almost wholly analgesic. There was also analgesia in each axilla. Touch was nowhere impaired and thermal sensation was not markedly involved. Wasserman's reaction was negative. The patient's pain was relieved by morphine. As soon as the vomiting stopped she was given small quantities of milk every two hours.

During the next five days she had only two attacks of nausea and vomiting. She began to have a good appetite and to feel better. Her blood pressure varied between 175 and 215 mm. until the 18th. On the 19th it was found to be only 120 mm., and since then, during the past ten days, the maximal pressure has varied between 110 and 125 mm.

In spite of the active knee jerks, the character of the vomiting, together with the sluggish pupils, and the analgesia of the legs made the diagnosis of tabes seem probable. This diagnosis receives support from (1) the extreme hypertension due to arterial spasm accompanying the attack, and (2) the results of the examination of the spinal fluid, namely, the increased lymphocyte count and the protein content.

We find attacks of severe abdominal pain similar to those present in this case in three distinct diseases:

I. Lead poisoning (abdominal colic).

II. Angina abdominis associated with arterio-sclerosis of the abdominal blood vessels.

III. Gastric crises of tabes.

In the preataxic stages of tabes we find a high blood pressure associated with the attack of abdominal pain and vomiting, while a low pressure is usually to be found in cases of tabes complaining of lancinating pains in the legs. The causation of the pain in the gastric crises of tabes has been much discussed. It seems probable that it is due to the irritation of the dorsal root fibers causing a reflex vaso-constriction in the splanchnic domain. According to Pal's theory the smaller vessels are constricted, and the high pressure on the arterial walls proximal to the area of constriction stretches the nerve plexuses in the vascular walls and causes the agonizing pain.

November 15, 1909.

Meeting of The Johns Hopkins Hospital Medical Society, Dr. Louis Hamman in the chair.

I. Exhibition of Surgical Cases. Dr. John W. Churchman.

Case I. *Typhoid Osteomyelitis.*—Boy aged fourteen years, with history of an attack of typhoid fever fourteen months ago. The patient recovered from the fever but was left with a typhoid spondylitis which is still present.

A few weeks ago he returned to the hospital with a symmetrical swelling in the region of the tibial tubercle on each leg. These lumps are easily palpable and slightly tender.

"X-ray" plates show that the condition is undoubtedly one of osteomyelitis, situated in the epiphyses from which the tubercle develops.

The osteomyelitis was of typhoid origin, and of a low order of infection, as proved by a bacteriological examination. There are no signs at present of an acute stage of inflammation; no granulations were found. These symmetrical lesions are very rare, especially in the present site, for typhoid osteomyelitis is most frequently found in the ribs in adults. At operation the bone was exposed and in the area of the swelling the bone had not yet completely ossified. The left side showed a small defect, apparently the remains of an old cloaca.

It is interesting to recall that Roswell Park called attention to the fact that after typhoid fever there is often marked irritation of the osteogenetic centers, and great tendency for growth of the part especially in the epiphyses of the large bones.

Case II. *Anterior poliomyelitis.*—This patient, a young man aged 21 years, who came to the hospital 19 months ago with a marked contracture of the left lower leg, and functionless tibialis anticus and rectus femoris muscles. He has been under surgical treatment for the past year and a half, and has had several operations.

In brief, the first operation consisted in the transplantation of the sartorius muscle into the rectus femoris muscle. The leg was then put up in extension. At the second operation the external and internal hamstring muscles were divided, and the leg again put in extension. Attention was then directed toward the foot, which presented a marked degree of talipes valgus. A complete Phelps operation was performed and a transplantation of a slip from the extensor longus digitorum and the extensor longus hallucis into the paralyzed tibialis anticus done.

The combination of these operations gives a good functioning leg; the patient, who was entirely unable to use the leg in walking on admission, now walks quite well with a brace.

Dr. Churchman emphasized the fact that treatment should be begun from the very start to prevent the formation of contractures.

Operation is not indicated early, certainly not within the first year, as some of the muscles tend to recover their function. In all cases the functioning result is better than the anatomical result.

II. Exhibition of Case. Tuberculide. Dr. C. von Pirquet.

Dr. von Pirquet exhibited a most interesting case of tuberculide occurring in a child two years of age, who also showed a most marked positive cutaneous tuberculin reaction.

The so-called focus reaction first noted by Herd appears not only at the point of application of the tuberculin, but also in all of the areas of former injections. In this particular case about the points of injection, in addition to the "focus" reaction, several larger areas of the erythema multiforma type of cutaneous tuberculosis could be readily seen.

III. Discussion of Nephrotomy by the Silver Wire Method; with a Report of Two Cases. Dr. E. H. Richardson.

This paper will be printed in full in the Bulletin.

Discussion.

Dr. H. A. Kelly.—Mr. Max Brödel's work in the demonstration of the double vascular zones of the kidney has helped to simplify the operative technique of kidney surgery. We, as surgeons, are greatly indebted to him for his valuable contribution. I should like to hear from Mr. Brödel how he came to take up the investigation of this problem.

Mr. Max Brödel (in response to Dr. Kelly).—An artist should always have a clear conception of what he has to draw. He had, at times, found it necessary to do a good deal of original investigation before he could truthfully portray the object which he had to draw.

In this particular instance not finding sufficient knowledge on the distribution of the vessels in the kidney, he decided to work out the problem himself. Numerous celloidin injections were made, both of the arterial and venous systems. The results of these experiments Dr. Richardson has fully explained to you.

Mr. Brödel then, by means of blackboard sketches, showed just how he worked out the planes of arterial distribution. The determination of the direction of the incision in the nephrotomy operation was, curiously enough, suggested to him by attempting to pass a walking-stick through a thick privet bush.

Mr. Brödel noted how much more easily the cane could be passed through the bush if it was directed from the main trunks close to the ground and passed in an outward direction, than if one attempted to force the cane through the bush from without inward.

Believing the same would hold true in the passage of a blunt instrument through what he pleases to call the "renal forest of vessels," he decided that the proper direction should be from the pelvis outward to the cortex.

December 6, 1909.

Meeting of The Johns Hopkins Hospital Medical Society, Dr. Louis Hamman in the chair.

I. Conditions inducing Acapnia: a Phase of the Shock Problem. Dr. Yandell Henderson, **Professor of Physiology, Yale University, New Haven, Conn.**

"The regulation of the rate of alveolar ventilation in breathing depends under normal conditions exclusively on the CO_2 pressure in the respiratory center." Haldane and Priestly, in their experiments, subjected normal men to atmospheres varying widely in respect to the oxygen tension.

The respiratory movements of the subjects did not show any reaction to these variations, nor did the subjects themselves experience any alteration in their own condition. When the barometric pressure and the CO_2 content of the air breathed was altered, the respiration was found to vary in such perfect adjustment to these conditions that the tension of the CO_2 in the alveolar air was maintained nearly constant. The respiratory center is exquisitely sensitive to any rise in CO_2 pressure, and is equally sensitive to even a slight reduction in the tension of the CO_2 below the normal.

It has been known for years that vigorous artificial respiration is followed by a period of apnœa. This period of apnœa is due to the temporary lowering of the CO_2 tension of the arterial blood below the threshhold exciting value for the respiratory center, and Haldane and Priestly have found that in man this period of apnœa is not present when the air forcibly respired contains CO_2 at nearly the same tension as that of the alveolar air.

According to Miescher the period of apnœa may be said to

consist of two conditions, apnœa spuria and apnœa vera. The temporary inhibition of the respiratory center, through the stimulation of the afferent nerve endings of the vagi in the lungs, results in the former condition. Apnœa vera is caused by the over aeration of the center, by excessive pulmonary ventilation. The changes in the blood might consist in an over-oxygenation or in a reduction of its CO_2 content. The work of Haldane and Priestly, Miescher, Mosso and Fredericq have shown that when the CO_2 of the arterial blood is diminished apnœa vera results.

Crile has found in his numerous investigations on surgical shock that in 90 per cent of the subjects death was due to respiratory failure. "In many instances the heart was beating strongly and the blood pressure was fair, at the time respiration failed. The results of these experiments would go far to show that the diminution of CO_2 is a factor in surgical shock were it not for the fact that two other explanations of the regulation of respiration and causation of apnœa present themselves.

The first explanation is that respiration is essentially a reflex function, and that the center is the constant recipient of augmenting and inhibitory influences of afferent nerves; the other the hypothesis that surgical shock is but the exhaustion of the center by the stimulation of the afferent nerves. Recent investigations have tended to show that the excitement of the vasomotor center in asphyxia is caused rather by the excess of CO_2 in the blood than by the lack of oxygen.

The amount of CO_2 in the blood is diminished whenever the subject is under diminished barometric pressure, and this diminution is thought, by many observers, to be the cause for the disturbance of function present in the so-called mountain sickness. For this peculiar condition experienced by individuals when at great elevations, Mosso has suggested the term "acapnia" (from καπνός, smoke, literally smokelessness). Many writers have commented upon the similarity of surgical shock and mountain sickness.

It is becoming a well-established fact that acapnia immediately produces tachycardia, and, if long continued, always results in shock. It is quite possible through breathing exercises for an individual to acquire ability to voluntarily increase or diminish the rate of pulmonary ventilation. For many centuries these breathing exercises have been practiced in India, with the belief that the subject can gain control over the heart rate and other functions. It is possible for the subject to render himself insensitive to pain or even unconscious. A condition of mental exaltation and hallucination can be produced.

Discussion.

Dr. W. H. Howell.—I wish to express my great appreciation of Dr. Henderson's paper. While many of his views do not coincide with the views of orthodox physiologists, the great importance of his paper in bringing to the front and emphasizing the subject of the relation of acapnia to shock will undoubtedly open up a broad field for fruitful experimentation.

I must confess that I knew that Dr. Henderson was to speak on this subject, but understood his paper was to be delivered at a meeting two weeks from to-night, and I would then have come prepared and fortified to discuss the paper in open meeting.

In the case cited by Dr. Henderson of a man dying from a "Fourth-of-July accident," in which death could not be attributed to hæmorrhage or shock, I am sceptical to believe that the patient died of acapnia pure and simple.

It has not been my experience in animal experiments to have the period of apnœa preceded by a period of hyperpnœa, and in the majority of the cases I have found the vasomotor center to hold out to the end, as has been the experience of Dr. Crile. I should like to defend the orthodox view of the automaticity of the respiratory center. So far as I am aware that center is automatic.

Dr. William H. Welch.—I remember reading, in one of the old works on surgery, of the custom of having a patient perform forced respiration for a few minutes just prior to a minor surgical operation, such as the opening of abscesses, etc. The belief was that this forced respiration produced a lessened sensibility to pain.

II. A Season's Experience with Prophylactic Vaccination against Typhoid. Major F. F. Russell, U. S. A.

The adoption of antityphoid inoculation or vaccination under certain conditions appears to be warranted. The presence of epidemics so frequently seen in American cities and during the time of great international conflicts makes it desirable to adopt some method for protecting the uninfected. The utility of this protection against typhoid was readily demonstrated in the late campaigns of the British army in India and South Africa (Boer war). The occurrence of typhoid in those inoculated was one-half that among the uninoculated, and the inoculation reduced the mortality of the disease by one-half.

Following the injection of the vaccine a local reaction appears at the site of inoculation. This consists of a red, tender spot about the size of the palm of the hand, appearing six to eight hours after inoculation, and disappearing in forty-eight to seventy hours. Occasionally there has been some lymphangitis along the course of the lymphatics and slight enlargment of the axillary glands. No case of suppuration of the glands has been reported.

The constitutional symptoms are limited to a feeling of lassitude, headache and occasionally a mild diarrhœa.

The prevalent idea of the "negative phase" or period of increased susceptibility to the disease makes widespread inoculation impossible. The negative phase is quickly followed by a positive phase, the antibodies increasing rapidly. Twenty-four hours after the administration of small doses the positive phase can be demonstrated, and it is only when large doses are given that one obtains a prolonged negative phase. Wright advocates the giving of several moderate doses eight to fourteen days apart, rather than the giving of a single injection. The inoculation of these quanta induces an ample elaboration of anti-tropic substances (antibodies) without producing any severe constitutional reactions.

The bactericidal and agglutinating properties of the patient's serum are increased and a greater resistance to typhoid intoxication is established. Milder symptoms follow the injection of the second dose than after the first.

So far as it has been possible to ascertain, the protection lasts two or more years, although a few cases have been reported in which infection has taken place from three to six weeks after vaccination.

DISCUSSION.

DR. W. H. WELCH.—It is somewhat striking that the attitude of the people toward typhoid vaccination is different than that toward vaccination against smallpox. The fact that typhoid is not a very contagious disease may account in no small degree for the prevailing attitude. The comparison is hardly a fair one, since the vaccination against smallpox produces an enduring immunity, while in the case of typhoid the period of immunity is quite variable. Antibodies are produced, but as yet we have no index for determining just how much of an immunity we have obtained, other than exposure to the disease, at different periods after the inoculation.

The negative phase is practically a negligible factor, and is really not such a great obstacle. Results are much better, so far as question of mortality is concerned in the cases, where the patients have been vaccinated. A single dose does not give much immunity, but in cases where a second or even a third dose is given, quite a substantial immunity is obtained.

DR. W. W. FORD.—Castellani in his experiments advocates the giving of first, an injection of a culture of living typhoid organisms; this to be followed by an injection of the killed bacilli. In certain cases injections of mixed cultures of typhoid bacilli and bacilli of dysentery or typhoid and paratyphoid bacilli have proven efficacious.

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NOTES ON NEW BOOKS.

Surgical Diagnosis. By Edward Martin, M. D. Illustrated. Price $5.50. (*Philadelphia and New York: Lea & Febiger, 1909.*)

Dr. Martin has covered the ground of surgical diagnosis well in this volume of 740 pages, all of which is written by himself with the exception of brief chapters on Laboratory Diagnosis by Dr. Longcope, The Application of the X-rays by Dr. Pancoast, Gynecological Diagnosis by Dr. Auspach, Diagnosis of Nervous Affections by Dr. Weisenburg, and assistance in the chapter on the Eye from Dr. de Schweinitz. The author has considered all the more common surgical troubles critically, laying especial stress on the early clinical diagnosis, and as a text-book for students it will be received cordially by the profession.

A System of Operative Surgery. By Various Authors. Edited by F. F. Burghard, M. S., F. R. C. S., etc. In Four Volumes. Vol. II. Price $10.00 per volume. (*London: Henry Frowde and Hodder & Stoughton, 1909.*) *Oxford Medical Publications.*

The operations described in this volume are those for Tuberculous Affections of the Bones and Joints by Harold J. Stiles; for Hare-lip and Cleft-palate by Edmund Owen; for Cancer of the Lips and Face by G. Lenthal Cheatle; upon the Jaws and the Oesophagus by C. H. Fagge; upon the Tongue, Tonsils and Pharynx by H. T. Butlin; upon the Stomach by B. G. A. Moynihan; upon the Intestines by G. H. Makins; for Hernia by Arthur C. Barker; upon the Rectum and Anus by F. Swinford Edwards. The contributors have shown more judgment than is often seen in the amount of space devoted to their special chapters, and as a result, the volume is well proportioned. Each subject has been carefully and judiciously handled, and the better and more well-known operations fully described. There can be little doubt that much of the success of the volume is due to the editor's ability, and that his must be the credit for producing such a serviceable surgery. The work is abundantly illustrated, though many of the drawings are merely diagrammatic, and their quality is not as good as is to be found in many American text-books of a similar nature. However, they illustrate sufficiently well the different points brought out in the text. Otherwise the volume is an excellent piece of book-making.

Bier's Hyperemic Treatment. By Willy Meyer, M. D., and Prof. Dr. Victor Schmieden. Second Revised Edition, Enlarged. (*Philadelphia: W. B. Saunders Company, 1909.*)

This interesting subject is brought to the attention of the profession in an attractive and practical manner. The style of the

authors is easy and the many excellent photographs render the text readily understood. The authors are undoubtedly enthusiasts on the subject and have given much time to it. The success of Bier's hyperemic treatment depends upon a thorough knowledge and application of the proper technic. It is a treatment which demands a great deal of the surgeon's time and constant supervision by him and for this reason has doubtless proven unsatisfactory to many investigators. It has, however, a wide field of usefulness and every surgeon should be familiar with it. Although it is claimed that patients can be taught to apply the treatment themselves, this has been found unsatisfactory, except in a few cases. It seems to us it is essentially a treatment for a clinic or hospital where the patients can be under observation for a large part of each day. As a method for treating the various tubercular affections, while it is valuable, we do not think it will ever supplant the cast and brace treatment, for inexperienced hands these older methods will give excellent functional results, which is one of the advantages claimed for hyperemia. The average surgeon will never succeed in obtaining the results reported by Bier and the authors. Hyperemia, however, is well worth a permament place in our therapeutic armamentarium and the author's book should be read by all physicians who are desirous of keeping up with the progress of modern medicine. The statement by Meyer and Schmieden that hyperemia is not a panacea is certainly necessary, as otherwise one would be left under the impression that there was very little it did not do in combatting the various acute and chronic inflammatory diseases to which the human body is subject. HENRY W. KENNARD, M. D.

Introduction to Practical Chemistry for Medical, Dental and General Students. Specially adapted to meet the requirements of the Conjoint Boards Examination at the Royal College of Physicians and Surgeons, but suitable for general use in schools and for private students. By A. M. KELLAS, B. Sc., Ph. D., Lecturer on Chemistry at the Middlesex Hospital Medical School. (*London: Henry Frowde and Hodder & Stoughton, 1909.*)

This is one of the "Oxford Medical Publications"; like the majority of English text-books on chemistry it is written to prepare for a certain examination, hence is of little value for American conditions. Its contents are a few simple inorganic preparations, a brief treatment of qualitative analysis and a briefer treatment of quantitative analysis; the methods of qualitative separations are all old, and the subject is presented mainly in the old-time tabular form. E. RENOUF.

The Physician's Visiting List for 1910. Price $1.00. (*Philadelphia: P. Blakiston's Son & Co.*)

This visiting list, intended for the pocket of the busy practitioner, has succeeded where others have failed, for it is now in its 59th year of existence. It contains a calendar, a new table for calculating the period of gestation, table of signs, incompatability, poisoning, metric system, dose table, etc. Its appearance is neat.

Manual of Chemistry. A guide to lectures and laboratory work for beginners in chemistry. A text-book specially adapted for students of medicine, pharmacy and dentistry. By W. SIMON, Ph. D., M. D., Professor of Chemistry in the College of Physicians and Surgeons, in Baltimore, and DANIEL BASE, Ph. D., Professor of Chemistry in the Maryland College of Pharmacy. Ninth Edition, thoroughly revised. (*Philadelphia: Lea & Febiger, 1909.*)

The fact that this is the ninth edition of this comprehensive manual shows that it is so popular and well known that it needs little comment. It differs from all other manuals in the colored plates indicating the color of various precipitates of metallic and organic compounds. More important is the scope of the book, with introductory chapters on chemical physics, and the inclusion of inorganic, qualitative, quantitative and physiological chemistry in one volume. The volume contains 716 large pages, but to crowd the mass of information into this space requires a condensed style. The new edition, revised with the able co-operation of Professor Base, is a notable improvement on the previous editions because of the modern chemical theory introduced and the additions to the chapter on physiological chemistry.

E. RENOUF.

Organic and Functional Nervous Diseases. A Text-Book of Neurology. By M. ALLEN STARR, M. D., Ph. D., LL. D., Sc. D. Third Edition, Thoroughly Revised. Illustrated with 300 engravings in the text and 29 plates in colors and monochrome. (*New York and Philadelphia: Lea & Febiger, 1909.*)

The previous editions of this work have established its high place in the opinion of all who have had opportunity to use it and the present edition will, if possible, move it up a little higher in general estimation. Much additional matter has been added from the researches and experience of the author and from the literature of neurology. New chapters have been added on symmetrical gangrene, reflex neuroses, angio-neurotic œdema and trophic symptoms of mental disorders. Much new material has been added to the chapter on paresis, to the section on decompressive operations in diseases of the brain, and to the discussion on spasmodic neuroses. The mental symptoms of neurasthenia and psychasthenia are presented and under their treatment psychotherapy is admirably discussed. The space allotted to the functional nervous diseases has been doubled. All of these additions have added greatly to the value of the book and there is but little opportunity for criticism. What there is being more a matter of personal opinion than any real defect it does not seem proper to mention.

Dr. Starr has a very clear style of writing which makes his book delightful reading, and after looking up a certain point one is tempted to read on. To the student this is an extremely valuable characteristic which is unfortunately not always found in text-books prepared for medical students. The illustrations are very good and the general make-up of the book is excellent. We have nothing but praise to say for this edition which we hope will be even more successful than its predecessors. W. R. D.

Diseases of the Genito-Urinary Organs and the Kidney. By ROBERT HOLMES GREENE, A. M., M. D., and HARLOW BROOKS, M. D. Second Edition, Revised and Enlarged. Price $5.00 net. (*Philadelphia: W. B. Saunders Company, 1908.*)

This book is the conjoint product of a surgeon and a physician. Chapters on subjects not usually incorporated in books of this character have been introduced, such as as: "The Blood in Diseases of the Kidney'; "Ocular Manifestations of Renal Disease," and a chapter on "Bright's Disease" The portion devoted to methods of examination of patients and manner of taking histories is valuable to the student. In the chapter on "Acute Urethritis" the writers state as a result of their clinical experience that it is better to postpone local treatment until the acute stage has passed: this is usually the 4th to the 6th week after the onset of the disease. In view of the fact that a very large percentage of cases are cured by the institution of local treatment within a few weeks, this seems strange advice. Even in cases where a rapid cure is not effected we have never seen any harm result where treatment was rationally applied. The article on stricture of the urethra is very poor and contains many errors. For instance, they state that the majority of strictures occur in the membranous urethra. All other writers, as far as we are aware, are unanimous in their statements that strictures origina-

ting in this region are rare. Sir Henry Thompson searched the pathological museums of Europe and was unable to find one specimen with stricture in the posterior urethra. The above is only one of many statements with which we cannot agree. The portion devoted to diseases of the prostate could profitably be rewritten. We most strongly disagree with the authors that prostatic massage is best performed by rubbing around the prostate and avoiding all pressure over the gland. It is little wonder they do not seem very enthusiastic about the results to be obtained from prostatic massage. As a whole the book is distinctly below the average, particularly in the portions devoted to disease of the lower genito-urinary tract.

Studies in Rabies. Collected Writings of NATHANIEL GARLAND KEIRLE, A. M., M. D., etc. With an Introduction by WILLIAM H. WELCH and a Biographical Sketch by HARRY FRIEDENWALD. Testimonial Edition. (*Baltimore: The Lord Baltimore Press. 1909.*)

It is fitting that the papers of Dr. Keirle, who was the founder of the Pasteur Institute in Baltimore, and whose articles on rabies are of distinct value, should be collected in a volume for the benefit of the profession. Such a testimonial is a mark of esteem of the man, as well as of the worth of his work. The volume is an important contribution to American medicine in a branch to which little has been added by American doctors, whose opportunities to study it have not been limited. It is to be hoped that his example may stimulate others to pursue further investigations in this horrible disease, which frightens the public almost more than any other. Any more contributions in this country in regard to its control and treatment will be largely due to his initial studies.

A Text-Book of Genito-Urinary Diseases. By DR. LEOPOLD CASPER. Translated and edited, with additions, by CHARLES W. BONNEY, B. L., M. D. Second Edition, Revised and Enlarged. Price $5.00 net. (*Philadelphia: P. Blakiston's Son & Co., 1909.*)

The second edition of this well-known work has been changed only in minor details. More attention has been devoted to a discussion of acute and chronic urethritis.

For a volume of its scope the contents are complete and the subject matter well handled. It is a work well suited for students and both the author and translator deserve commendation.

Études Anatomo-Cliniques: Coeur Vaisseaux Poumons. Par DR. RAYMOND TRIPIER, Professor à la Faculté de Médecine de Lyon. 595 pages. (*Paris: G. Steinheil, Editeur, 1909.*)

The book is conceived in a spirit of protest against the tendency to separate sharply the studies of pathological anatomy and clinical medicine. Specialization is thought to have exceeded its just bounds, missing the fruits of an intimate correlation. Throughout these studies, anatomical considerations are closely interwoven with ingenious reasoning from clinical data. The material put before the reader, while not always convincing, is interesting. Most characteristic are the chapters on tuberculous endocarditis, arterio-sclerosis, and incipient pulmonary tuberculosis. To tuberculous endocarditis, the author gives a larger sphere than is usually conceded in similar works.

In the chapter on arterio-sclerosis, the author builds largely on his view that inflammation is really in large part a mechanical change consequent upon capillary obstruction. He dissents strongly from the views of Huchard. The vascular lesions in arterio-sclerosis are regarded not as the result of hypertension consequent upon renal changes, but secondary to changes in many organs due to the same cause that induced the renal lesion. Hypertension consequently is the result, not the cause, of arterio-sclerosis. Hypertension produces not degeneration, but hypertrophy of the heart, and hypertrophy alone is the usual finding in the *Brightique* hearts of young people, unless there is a history of previous infection such as might be sufficient to produce tissue changes in heart muscle.

The author's views on pathogenesis of pulmonary tuberculous lesions are redeemed by his radical but sound advice as to treatment. Tripier does not share in the prevalent but unjustified optimism as regards the prognosis of definitely recognizable pulmonary tuberculosis, and therefore urges treatment during the so-called pre-tuberculous stage. In this he touches upon a sore difference between those phthisotherapeutists who emphasize the frequent recovery of patients with well-established lesions, and those who have been distressed by the unfortunate outcome in some cases which have received treatment even before a diagnosis could safely be made.

S. W.

Proceedings of the Third Annual Conference of the American Association of Medical Milk Commissions. 1909. Cincinnati, Ohio.

This association, now in its fourth year, deserves support and endorsement. Its members are striving actively in their efforts to secure pure milk supplies all over the country, and thus to help in diminishing the mortality and morbidity which results from dirty milk. It is questionable whether there is any other food consumed so dirty as milk ordinarily is. It should be one of the first duties of health boards to enforce pure milk supplies, and this association is doing good work towards this end.

Diseases and Surgery of the Genito-Urinary System. By FRANCIS S. WATSON, M. D., etc. Assisted by JOHN H. CUNNINGHAM, JR., M. D., etc. Illustrated. 2 vols. Price $12. (*Philadelphia and New York: Lea & Febiger, 1908.*)

This work is in two volumes and is by far the most complete and thorough treatise on diseases of the genito-urinary tract published in English.

The first volume is devoted to the external genitals, prostate and bladder, while the second volume deals almost solely with the kidney. Tuberculosis of the genito-urinary tract is considered as a whole in a chapter at the end of the second volume. This seems a very rational method of handling the subject instead of considering it in a fragmentary manner under diseases of the prostate, again under testicle, bladder, etc. Various portions of the tract are so frequently involved at the same time that the student can only get a clear concept when the disease is considered as a unity.

An unusual amount of space has been devoted to the description in detail of operative procedures. The illustrations in the work are good and the photographs of specimens showing prostatic hypertrophy are splendid.

Possibly for use of the average student sufficient space has not been devoted to the minor subjects. The authors have evidently devoted time and study to the preparation of the volumes, furnishing each section with a good bibliography and have produced a work which is to be highly commended.

The work impresses one as being the product of men with a familiarity and thorough grasp of the subjects handled.

Biographic Clinics. Volume VI. Essays Concerning the Influence of Visual Function, Pathologic and Physiologic, upon the Health of Patients. By GEORGE M. GOULD, M. D. (*Philadelphia: P. Blakiston's Son & Co., 1909.*)

We regret to learn from the author in the first chapter that "This forelying sixth volume of Biographic Clinics will be the last I shall write. To the gospel I have given all the strength

and money I could spare and of both the expenditure has been great." Those who have read the previous volumes cannot help regretting that we are not to have similar pungent essays and trenchant statements as to the effect of errors of refraction upon the health of patients. Granting that like all other souls crying in the wilderness the author has at times seemed impatient of the slow progress of his evangel, no one can aver that he has not brought about great results. The attention of physicians and others has been directed to this potent cause of ill-health and it is now the custom to seek diligently for errors of refraction in the study of all cases of obscure disease. The injurious effect of uncorrected astigmatism upon bodily function is now generally acknowledged, and for the acceptance of this addition to our knowledge we are largely indebted to Dr. Gould. The zeal of the accomplished author sometimes betrays him into a vehemence of expression not wholly in harmony with an exposition of scientific truth. While this may add to the vigor of the book, it does not add to the permanent effectiveness of the appeal and is to be deplored. "The Case of Jonathan Swift" and "The Pessimist—Added Testimony in Wagner's Case" are valuable contributions to the life histories of well-known men and of equal interest to similar biographies of Carlyle, Elizabeth Barret Browning and others in previous volumes.

A Manual of Otology. By Gorham Bacon, A. M., M. D., Professor of Otology in the College of Physicians and Surgeons, Columbia University, New York. With an introductory chapter by Clarence J. Blake, M. D., Professor of Otology in the Harvard Medical School, Boston. New (5th) Edition, Thoroughly Revised. 12mo. 500 pages. 147 engravings and 12 plates. Cloth, $2.25 net. (*Philadelphia and New York: Lea & Febiger, 1909.*)

We have previously reviewed this excellent little manual and it is a pleasure to note that the author has so soon been called upon for another edition. The book fully covers the needs of general medical students and family practitioners of medicine and deserves the favor it has received in these fields. The introductory chapter, pointing out the importance of this special branch of medicine and the relationship of otology to general medicine should have the consideration of every physician.

The alterations in the new edition, bringing the whole work quite up to date, are a pleasing feature and Dr. Bacon is to be congratulated upon having presented the students with one of the most complete and compact manuals in the English language.

H. O. R.

The Medical Complications, Accidents and Sequels of Typhoid Fever and the Other Exanthemata. By H. A. Hare, M. D., B. Sc., Professor of Therapeutics in the Jefferson Medical College and Physician to the Jefferson College Hospital, Philadelphia, and E. J. Beardsley, M. D., L. R. C. P., Philadelphia. With a special chapter on the Mental Disturbances Following Typhoid Fever, by F. X. Dercum, M. D., Professor of Nervous Diseases in the Jefferson Medical College. Second Edition, Thoroughly Revised and much Enlarged. Illustrated. Price $3.25. (*Philadelphia and New York: Lea & Febiger, 1909.*)

The second edition of this book differs from the first in the addition of new chapters on the complications, etc., of variola, scarlet fever, measles, varicella and rubella; and an excellent chapter by Dr. Dercum on the mental disturbances following typhoid fever. The work is a useful one, but has not been prepared with sufficient care. For instance in the chapter on rubella, there is only one reference since 1900, and most of them are much earlier. The typesetting also in this chapter does not agree with that used in the other chapters. There is still one severer criticism to be made of the work as a whole. The bibliography throughout has been prepared in a slipshod manner, entirely wrong references are given—both as regards titles and dates—the latter being frequently omitted. There is no general system of abbreviations used, and the misprints in the titles of foreign journals are inexcusably bad; there are wrong spellings, accents, capitals and punctuation. The errors are numberless; the reviewer has not taken the trouble to look up each individual reference, for the mistakes are self-evident. Important references that should be given are entirely omitted. In a work of this nature, where it is all essential that the references should be correct, such a bibliography has no excuse, and injures the value of the book for all students. It is to be hoped that a third edition will be "thoroughly revised."

A Text-Book of Special Pathology for the Use of Students and Practitioners. By J. Martin Beattie, M. D., Professor of Pathology and Bacteriology, University of Sheffield, etc., and W. E. Carnegie Dickson, M. D., Lecturer in Pathology and Bacteriology, and Senior Assistant to the Professor of Pathology in the University of Edinburgh, etc. Price $5.00. (*Philadelphia: P. Blakiston's Son & Co., 1909.*)

The authors say in their preface, "If any excuse were necessary for adding another to the many text-books of pathology, it would be found in the fact that the present volume is based on the teaching of the Edinburgh School." There can be no doubt concerning the influence which this school has had in moulding pathological opinion and inasmuch as this book deals with pathological problems as they are conceived by that school, led at present by Dr. Greenfield, it will be read with interest by the pathologist and the student.

The book corresponds in its scope to the numerous special pathologies intended for the student and practitioner already on the market. Its arrangement presents nothing radically opposed to what we are accustomed to find in works of this nature. It is written in an exceptionally clear and logical manner so that the reader readily grasps the underlying thought and best of all it is elaborately illustrated by splendid photographs of typical morbid conditions. These deserve special mention since they are not the old hackneyed pictures one is accustomed to see in books of this nature. The photomicrographs are exceptionally clear and illustrative.

The relation of the gross and microscopic pictures of morbid conditions, probably one of the most difficult obstacles for the student to conquer, and also an extremely difficult subject to be explained by descriptive writing is only briefly dealt with.

At the beginning of many chapters a brief résumé of the normal anatomy and histology is found which will be of great assistance to the student. He finds, for instance, a clear and concise description of the normal structural arrangement of the complicated system of renal tubules, vessels, etc., before the pathology of this organ is considered and again before the discussion of malformation of the heart and great vessels is entered upon one finds a brief description of their embryonic development which is so necessary for the proper understanding of their malformations.

The discussion of some rather difficult problems is particularly clear. Among these it is of interest to note that the authors consider Hodgkin's disease a distinct clinical and pathological entity entirely independent of the tubercle bacillus, and to be rather of the nature of an infectious granuloma than a new growth. They describe the condition practically in the manner of Miss Reed, though they do not quote this author and yet quote in detail the later work of Longcope.

Concerning the nature of the pathological change in the liver cells consequent upon chronic congestion, the authors still consider the disappearance of the cells about the hepatic vein as a pressure atrophy. They do not mention the retrojection of bile among the etiological factors of hemorrhagic pancreatitis, and in

general this chapter is unsatisfactory. From the statement that absence of the pancreatic secretion interferes with the absorption of fatty substances in the intestines and in such cases the stools contain excess of undigested fat, one would hardly believe that this question is still in a very chaotic condition; again in their experience cancer of the head of the pancreas is rare, while it is generally considered to be rather frequent.

In the discussion of the ductless glands the distinction between the function of the parathyroids and thyroid glands is not sufficiently emphasized, nor is the relation of lesions of the adrenal to Addison's disease discussed to the extent our present knowledge would allow.

Briefly, the book is for the most part a clear exposition of the field of special pathology. While in scope it corresponds to many other books of the same order, it is well written, very well illustrated and will no doubt be of real use to the student of pathology, especially in those schools where the thorough system of the Edinburgh School has been adopted.

Arthritis Deformans: Comprising Rheumatoid Arthritis, Osteo-Arthritis and Spondylitis Deformans. By R. Llewellyn Jones, M. B. (Lond.). XIV, 365 pages. (*Bristol: John Wright & Sons Ltd., 1909.*)

There is so much obscurity connected with the subject of chronic arthritis that it is not an easy task to discuss it clearly and satisfactorily, and any work which does this is welcome. The majority of French and German writers on this subject cannot be said to have produced illuminating articles; they rather complicate the question than render it clear. Dr. Jones has given us a clear discussion of the subject. He has had excellent opportunities for the study of arthritic maladies. Living in Bath, to which for centuries invalids have repaired and where those suffering from arthritis go in large numbers, he has had the advantage of study in a hospital to which many patients with arthritis are admitted, and also of seeing many patients from elsewhere. The importance of increasing our knowledge of arthritis deformans is great. Not a disease which kills but one which cripples and incapacitates, every effort to learn more as to its nature and how to limit its power for harm must be welcomed. It may be said here that Dr. Jones has given us an excellent work on the subject.

After a historical review in which the ancient history of the disease is discussed he takes up the question of classification and supports strongly the view that under the heading arthritis deformans there are two distinct diseases, rheumatoid arthritis and osteo-arthritis. On this point there is great difference of opinion and recent articles illustrate this. Thus Garrod, in the article in Allbutt and Rolleston's System of Medicine, takes the same view, while McCrae, writing in the Osler System, takes the opposite position, that the various forms are differing manifestations of the one disease. Important support of this latter view is the frequency with which lesions characteristic of the two forms are found in the same patient. Dr. Jones considers this as the co-existence of two diseases, just as gout and arthritis deformans may be seen together, but this is exceedingly rare, while the commonness of the occurrence of the two forms of arthritis in the same patient is against this. There is evidence of the difficulty of the author's view in the discussion of spondylitis deformans. For convenience of description this is discussed separately from rheumatoid arthritis and osteo-arthritis, but the author points out that "no sharp line can be drawn between it and the peripheral types of arthritis deformans, owing to the existence of endless intermediate or transitional forms." Dr. Jones, in discussing the etiology of spondylitis, speaks of the rigidity being "the result either of rheumatoid arthritis or osteo-arthritis." It is "the existence of endless intermediate or transitional forms" which renders it difficult to accept a sharp division of the whole group into two diseases.

Taking the view that there are two diseases the author naturally discusses them separately. The description of the symptoms is excellent throughout and especial attention, and most properly so, is given to the early symptoms. The importance of the careful study of these as an aid in the early diagnosis, so important for correct early treatment, cannot be overestimated. The question of treatment is well discussed and drug therapy is not unduly exalted.

The work is to be very heartily commended as probably the best discussion of the disease we have. The enormous literature on the subject has been well handled and it is a pleasure to see that the American literature has been carefully considered. The publishers have done their work well and the page and illustrations are alike good.

Tuberculosis. A Treatise by American Authors on its Etiology, Pathology, Frequency, Semeiology, Diagnosis, Prognosis, Prevention and Treatment. Edited by Arnold C. Klebs, M. D. With three colored plates and 243 illustrations in text. (*New York and London: D. Appleton & Co., 1909.*)

There are a number of things about the book that do not please the reviewer. Others may not share his views and perhaps they are the result of personal peculiarity, but he neither expects nor seeks to elicit agreement. Most prominently disappointing is the arrangement of the bibliography. It would be much more valuable if each section were followed by its appropriate list of references and still more useful and convenient if they were added as footnotes at the bottom of the page. It is a source of constant annoyance to be obliged to turn to an alphabetical index when a judicious quotation or an important reference arouses a curiosity to know its source. After considerable investigation the reviewer is unable to say just what scope the bibliography was meant to have. It is more than a compilation of the works cited in the text and far less than anything like a complete list of tuberculosis literature. Apparently the plan was to include all publications by contributors to the volume whether they are quoted or not and to add such other references, important or otherwise, as are fortunate enough to have been mentioned. What practical use this scheme subserves it is difficult for one disinterested to understand. I take the instance of Knopf as an example merely because it represents most flagrantly what is meant. In the text he is directly cited not more than three or four times, yet in the bibliography there are fifty-six references to his writings. Now it is an important matter to have a complete list of the publications of Dr. Knopf and every student of tuberculosis literature will be duly grateful for the compilation. However, it does not seem clear why he is so honored when others, may I say equally prominent, and then name Koch, Behring, Römer, Turban, Möller, Bandelier, Röpke, Calmette, Arloing, Courmont, etc., are slighted.

As an addendum to each section there is a summary of the papers upon this particular subject presented at the International Congress, held in Washington, D. C. In no instance do these summaries add anything of importance or even of interest to what had previously been written. Did they contain such valuable additions, proper emphasis could be given them only by incorporation in the text. They lend the book a superficial air of unusual up-to-dateness which in substance they do not sustain.

The same remark might be applied to the brief introductory paragraphs written by prominent authorities. They add the glamor of a great name, but do not enhance the value of the book. We do not question the motive that led to their insertion, but the effect is to create the impression that they were added to give a stamp of authoritative co-operation and approval.

The notes by v. Pirquet on tuberculosis in childhood, while in

themselves excellent, seem scarcely appropriate as an introduction to the section on symptomatology and diagnosis. Still it is hard to say where they would be appropriate and so they might as well be placed here as elsewhere. Why they were added the editor tells us in an ingenious foot-note which, viewed from a certain standpoint, is not without humor. It might be questioned whether it is wise to exploit the general interest in our most recent American acquisition. I should certainly not dare to give the answer. A very celebrated artist has created a remarkable effect by filling a void in his most celebrated painting with two cherub heads which are popularly known as the "afterthought." v. Pirquet's article is an editorial "afterthought" and opinions might vary from one considering it an excellent but incongruous insertion to another looking upon it as a rare and brilliant inspiration.

The historical sketch is written in Osler's terse and pregnant manner. The etiology by Ravenel is notable for the author's restraint. Where so many controversial points are touched it is difficult for one interested in all their details to resist discursiveness. The matter is forcefully and judiciously presented. Fault can be found only with the heated attitude assumed towards Koch. Granting that he be wrong in his contention that bovine tuberculosis is a negligible factor in human infection, it would still be the part of valor to treat so distinguished an opponent with gentleness and consideration. Hektoen's chapter on pathological anatomy is remarkable. Astonishment ever increases at the amount of matter compressed in so small a space. It is not easy to read, does not flow smoothly, but there are few unnecessary words and not a superfluous sentence. Even subsidiary clauses often suggest a paragraph of important matter. Baldwin gives a good summary of the factors of immunity in tuberculosis, but to those interested in these problems, far too concise. On special phases of the subject he has elsewhere written far more thoroughly and entertainingly. A text-book naturally imposes restrictions which add great difficulty to a proper presentation of so intricate a subject.

The section by Klebs contains all the essential information on mortality and morbidity. Coleman reviews the special conditions relating to tuberculosis among the Negroes and Indians and Hutchins among the insane.

The section on symptomatology and diagnosis, the largest and most important in the book, is written by Minor. The arrangement is excellent and although it necessitates a certain amount of repetition, the importance of the points reiterated makes it impossible to emphasize them too frequently. The style is in places involved. As an example, reread the opening paragraph. Too frequent quotations detract somewhat from the force of personal views and could with benefit be omitted, or else added as footnotes. They often force the impression of literary display which is evidently far from the author's purpose. It seems, however, unnecessary to seek the support of authority for everyday observations. I can make my meaning plainest by a quotation from Jules Lemaitre. Speaking of the oratory of Le Père Monsabré he writes: "The Père somewhat abuses citations from Saint Thomas. In his first conference he finds it necessary to invoke him to tell us that penitence is to the soul what medicine is to the body. The thought, however, is in no way extraordinary; the author should, I believe, have been able to hit upon it himself. One does not derange a saint for so little." Allowing that many of the authors quoted do not possess in medicine the same imposing authority that St. Thomas does in theology, the remarks are otherwise pertinent and we may justly say that the author somewhat abuses citations. Quite naturally, there are a number of minor preferences expressed with which all will not agree. I mention among others the value of the cyrtometer in diagnosis, the necessity of using the little finger as the pleximeter in apical percussion, and the superiority of fluoroscopy over radiography. We believe too that percussion resistance is felt earlier than the author admits. But these differences are trivial in the light of the general excellence of the presentation. The remarks on hemorrhage are strikingly good. It is refreshing to see inspection and percussion restored to their proper position of importance in early diagnosis. The chapter on the method of examination could not be improved. Indeed, all in all, it is the most satisfactory treatment of the subject in English with which the reviewer is acquainted.

Individual prophylaxis is satisfactorily reviewed by Baldwin. Knopf treats public prophylactic measures in his usual full and enthusiastic manner. His caution that the popular lecture should not exceed three-quarters of an hour may provoke a smile.

Brown has written a most comprehensive chapter on specific treatment and one which shows at every point his intimate acquaintance with all phases of the subject. He assumes a moderate and a very open attitude towards tuberculin. The fundamental principles of treatment are thoroughly reviewed, although the theoretical discussions lack precision and clearness. Some of the statements it is difficult to reconcile. He says Wright's method is a step in the proper direction and on the following page that in practice it may be disregarded. He asserts that the results of tuberculin immunization have never been as striking as those attained by small repeated doses of tuberculin, while later he admits that many have not been able to substantiate these results. While granting that there is little difference between the action of the various tuberculins, he advances reasons why a mixture of B. F. and B. E. is to be preferred. This author also has a tendency to abuse citations.

Webb gives a brief but excellent account of the vaccine treatment of secondary infections.

The chapter on the hygienic, dietetic and symptomatic treatment is far too brief. It occupies but forty pages, while climate is allowed fifty-seven. It is a good practical exposition, but diet particularly lacks the scientific detail that a modern treatise should give. Klebs has a good account of the management and construction of sanatoria.

The physiology of climate is well presented by Sewall, but the knowledge gained will add little in its practical application. Barlow takes a refreshingly moderate view about the value of climatic therapeutics.

The whole subject of surgical tuberculosis is written by Freeman and McArthur. The consideration of the individual subjects is necessarily brief, and indeed in proportion to their importance some of them disappointingly brief, notably tuberculous peritonitis. A separate section on serous membrane tuberculosis would be desirable.

The list of prescriptions at the end of the book should, if important enough, be given their proper position in the chapter dealing with treatment. Loosely thrown together they are of little value and they may do a great deal of harm. They are certainly not written in the spirit of modern therapeutics.

In conclusion, a word about the impression the book as a whole makes. The work of the contributors is for the most part well done and they have succeeded in producing a truly valuable work. With such alterations as the foregoing remarks suggest, the reviewer would not hesitate to pronounce it excellent. L. H.

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CONTENTS.

STUDIES ON ISOAGGLUTININS AND ISOHEMOLYSINS.

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The hemoglobin may be set free from the red blood corpuscles by a variety of influences; as mechanical injury, extremes of temperature, variations in the tonicity of the medium in which they are placed, acids, alkalies, soaps, bacterial and other plant hemotoxins, etc. Likewise corpuscles agglutinate under a variety of influences but in the work to be reported in this paper care has been taken to exclude all agglutinating and hemolysing influences except those possessed by the serum.

Serum agglutinins and hemolysins may be designated as normal and immune, according as they exist in the blood of animals in their natural state or have resulted from the artificial introduction of blood from one animal into another. The serum of many animals normally possesses the power of agglutinating and dissolving the corpuscles of animals of a different species, due to the presence of normal heteroagglutinins and heterohemolysins. This power may be greatly increased by the injection of foreign red blood corpuscles, the immune heteroagglutinin and heterohemolysin thus produced, however, being in a high degree specific for the particular kind of red blood corpuscles used in their production.[1]

The prefix iso- is used to designate that variety of agglutinin and hemolysin which is effective against the erythrocytes of another animal of the same species as that possessing the agglutinin and hemolysin. Isoagglutinins and isohemolysins may be normal: i. e., occurring naturally; or immune, resulting from the injection of red blood corpuscles of an animal into another animal of the same species.

Auto- is the prefix applicable to agglutinins and hemolysins capable of clumping and dissolving the corpuscles of the animal possessing such "bodies." We have a well recognized example of autohemolysin in certain forms of paroxysmal hemoglobinuria, but with the peculiarity that the amboceptor unites with the corpuscles only at certain low temperatures while the complement does not combine except at higher temperatures.

This paper deals with normal isoagglutinins and isohemolysins occurring in the serum of man. Ehrlich and Morgenroth (Studies on Hemolysins. Berlin. klin. Wchnschr., 1900, No. 21) were able to produce isohemolysins in animals by the injection of the blood of one goat into another, but in no case were they able to demonstrate autohemolysins following the injection of an animal with its own corpuscles.

[1] It is likely that the normal agglutinin and hemolysin are also specific. If one takes a serum which is able to agglutinate or hemolyse two different varieties of corpuscles and allows it to act on a sufficient quantity of one variety, all of the agglutinin or hemolysin for that variety can be absorbed without lessening the ability of the serum to agglutinate or hemolyse the other variety of corpuscle.

A few observers have reported the finding of normal isoagglutinins and isohemolysins in animals, but their occurrence is rare as compared with the frequency with which they may be found in man. Indeed Hektoen (J. Infect. Dis., 1907, Vol. IV, p. 297), states that he has "not been able to find any isoagglutinins in the serum of rabbits, guinea-pigs, dogs, horses, and cattle," although "the serum of the majority of healthy individuals above six years of age contains isoagglutinins."

Numerous attempts have been made to establish some relation between the occurrence of isoagglutinins and isohemolysins, and various diseases, but so far the claims of investigators who maintain that such relations exist are not borne out by the accumulated evidence. It seems likely that the misleading results of many of these observers have been due to the fact that they have based their conclusions upon the action of the sera investigated upon corpuscles from too small a number of individuals, for it has been definitely established that a given serum may agglutinate or hemolyse the corpuscles of certain individuals and not those of others, so that the results obtained in any series of cases would depend largely upon the corpuscles employed in the test. For this reason, in all of my investigations, the serum of each member of a series was tested against the corpuscles of every other member of the series; and the occurrence or absence both of agglutination and hemolysis noted.

Furthermore certain of the discordant results probably have been due to variations in the technique used. Some of the earlier observers were content merely to bring together equal quantities of the defibrinated blood of two individuals and observe the results. In such tests the possible interaction of four elements was present; namely, two different sera, and two different kinds of corpuscles, instead of the action of a single serum on a single kind of corpuscle; a matter of importance, as will be shown later, on account of the inhibiting action which certain sera are capable of exerting on hemolysis.

The technique employed in all of the tests here reported was carried out with surgical asepsis, and great care was taken that the syringe, pipettes, test-tubes, and all glassware used were not only sterile but very clean. Blood is taken from a vein at the elbow. For this purpose the skin over the vein is rendered aseptic and about 20 cc. of blood is withdrawn by means of a syringe which previously has been boiled and then washed out with a solution containing 1.5 per cent sodium citrate and 0.85 per cent sodium chloride; this removes any water which remains in the syringe after boiling and which might cause slight laking of the blood. Two sterile centrifuge tubes are ready to receive the blood as soon as it is withdrawn, one being empty and the other containing 10 or 12 cc. of 1.5 per cent sodium citrate in 0.85 per cent sodium chloride solution. Into the tube containing the sodium citrate, 3 cc. of blood is introduced for corpuscles, and the remaining blood is put into the other tube for serum. The corpuscles are further prepared by centrifugalizing them out of the sodium citrate solution, pipetting off the supernatant fluid and washing them twice with 0.85 per cent sodium chloride solution to free the cells from serum. After the last centrifugalization, which is continued until the cells are thoroughly sedimented, the supernatant fluid is pipetted off and 0.5 cc. of the corpuscles is transferred to 9.5 cc. of 0.85 per cent sodium chloride solution, thus making a 5 per cent suspension.

The tube containing the blood for the serum is allowed to clot and after about half an hour the clot is carefully separated from the sides of the tube with a sterile platinum needle, after which the serum is easily obtained by a few minutes' centrifugalization. The clear serum is then pipetted off from the clot and transferred to another tube. Serum and corpuscles are similarly obtained from a number of individuals.

The further proceedure consists in combining equal quantities (usually 0.25 or 0.5 cc.) of serum and suspension of corpuscles so that the action of each serum is tested on the corpuscles of every member of the series separately These mixtures having been made, the tubes are shaken to distribute the corpuscles evenly through the serum, and are then allowed to stand in the thermostat at 37.5° C. for 2 hours, after which they are placed in the icechest over night. Readings are made at the end of the two hours in the thermostat and after the tubes have stood over night in the icechest. Agglutination and hemolysis are easily determined by the naked eye, and the results of the reading at the end of two hours in the thermostat and after having stood over night in the icechest differ, if at all, only slightly in amount.

Before examining the results obtained, it may be stated that no constant differences were found between the agglutinating or hemolysing abilities of sera in health and in disease. The serum of a healthy individual might agglutinate or hemolyse the corpuscles of some healthy individuals, but fail to agglutinate or hemolyse those of other healthy individuals, and the same variations were noted in its action on the corpuscles of patients suffering from a variety of diseases. The same relations were found to exist between the serum in disease and the corpuscles of diseased and healthy individuals. Tests have been carried out on the blood of 213 individuals of whom 97 were healthy, and 116 diseased. In the case of 22 of the healthy individuals the blood was tested from two to 5 times, at intervals of a few days, weeks, or months. The agglutinating action of these sera was found to be constant, but the hemolytic power varied in some of them from time to time. On five occasions series of 20 individuals were tested. In these series the serum of each individual was tested against the corpuscles of every other individual, including his own—a total of 400 tests in each series. Certain results were obtained from these large series which might have been missed in smaller ones.

In about half of the total number of cases examined the tests were carried out on groups of eight individuals at a time, the serum of each one being tested against the corpuscles of each member of the series, making a total of 64 individual tests. When examining patient's blood, the serum was often tested against corpuscles from a number of normal in-

dividuals. The ability of patient's serum to hemolyse and agglutinate normal corpuscles; of normal serum to hemolyse and agglutinate patient's corpuscles; and furthermore the presence or absence of autolysis and autoagglutination in both patients and normal blood was noted.

It would require too much space to include here the individual results, but they have been summarized and are tabulated in convenient form.

TABLE I.

No. Cases.	Disease.	Pat. Serum. Nor. Corps.		Nor. Serum. Pat. Corps.		Pat. Serum. Pat. Corps.		Nor. Serum. Nor. Corps.	
		Hem.	Aggl.	Hem.	Aggl.	Autol.	Autoaggl.	Autol.	Autoaggl.
35	Tuberculosis. Various forms....	8	14	7	10	0	0	0	0
27	Carcinoma..........	4	6	6	8	0	0	0	0
14	Typhoid fever.....	3	5	1	5	0	0	0	0
10	Chronic nephritis..	1	3	2	4	1	0	0	0
6	Diabetes mellitus..	0	2	3	2	0	0	0	0
5	Pernicious anemia.	1	0	3	2	0	0	0	0
4	Lues	1	2	0	0	0	0	0	0
83	Other diseases	8	24	12	25	0	0	0	0
		26	56	34	56	1	0	0	0

Examination of Table I shows that normal serum was able to hemolyse and agglutinate patient's corpuscles as often as patient's serum was able to hemolyse and agglutinate normal corpuscles; that this relation does not differ markedly in different diseases, and furthermore that autoagglutination did not occur in a single instance, while autolysis occurred only once. This latter case requires closer examination. The blood was from a chronic nephritic who was in uremia at the time the test was made. The solution of his corpuscles was but slight in extent and not accompanied by agglutination which leads me to think that the hemolysis was not due to a specific amboceptor-complement action, but perhaps to some toxic substance circulating in the blood, of a chemical nature.

The serum of this patient not only hemolysed his own corpuscles, but those of all of the seven other individuals against which it was tested, and in no case did it cause agglutination.

We have seen thus far that the agglutinating and hemolysing action of patient's serum on normal corpuscles does not differ in any marked degree from the action of normal serum on patient's corpuscles. In order to complete this study, it is necessary to investigate the action of normal serum on normal corpuscles and of patient's serum on patient's corpuscles. For this purpose two series of 19 patients each, suffering from a variety of diseases were taken and the serum of each one was tested against the corpuscles of every other member of the series as well as the autogenous corpuscles. Similarly three series of 19 or 20 healthy individuals were tested.

The results are given in Tables II and III. They show no important differences between the action of patient's serum on patient's corpuscles, and the action of normal serum on normal corpuscles. Furthermore these two reactions—patient's serum on patient's corpuscles and normal serum on normal corpuscles, do not differ markedly from the relations brought out in Table I where patient's serum was tested against normal corpuscles and normal serum against patient's corpuscles.

TABLE II.

	Number whose serum agglutinated or hemolysed the corpuscles of one or more members of the series.	
	Agglutinated.	Hemolysed.
1st Series 19 patients.	18	1
2d " 19 "	17	8
38	35	9

TABLE III.

	Number whose serum agglutinated or hemolysed the corpuscles of one or more members of the series.	
	Agglutinated.	Hemolysed.
1st Series 20 normals.	19	11
2d " 20 "	18	0
3d " 19 "	16	3
59	53	14

From Tables II and III we see that of 59 normal sera tested, 53 (89+ per cent) agglutinate and 14 (23+ per cent) hemolyse as compared with the sera of 38 patients in which 35 (92+ per cent) agglutinate and 9 (26+ per cent) hemolyse, from which we may draw the conclusion that there is no marked difference between the isoagglutinating or isohemolytic action of the serum in health and disease, and while some still claim that one or the other of these reactions may be made use of in the diagnosis of various diseases, I must agree with those who maintain that they have no diagnostic significance. It is true that the individual series in any one disease here studied is not large, but collectively they seem sufficient for the above generalisation.

Certain other points in regard to isoagglutinins and isohemolysins, perhaps, only of theoretical interest, have been studied in some detail.

Landsteiner (*Ueber Agglutinationserscheinungen normalen menschlichen Blutes.* Wien. klin. Wchnschr., 1901, XIV, p. 1132) in 1901 denied the specificity of the isoagglutination reaction for disease and pointed out that the phenomenon is also produced by the serum of healthy individuals and goes so far as to attempt a classification of sera according to their isoagglutinating action. His classification, which has been generally accepted up to this time, makes three groups as follows: "In a number of cases (Group A) the serum agglutinates the corpuscles of another Group (B) not, however, those of Group A; while the corpuscles A are agglutinated by the serum B. In the third Group (C) the serum agglutinates the corpuscles of A and B." That this classification is imperfect is shown by attempting to apply it to any of the series of 20 individuals in which I have tested each serum against the corpuscles of every member of the series.

One such series will suffice to point out the difficulties of its application.

TABLE IV.

SERUM. / CORPUSCLES.

No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1					+		+	+	+		+	+		+	+		+			+
2					+		+	+	+		+	+		+	+		+			+
3					+		+	+	+		+	+		+	+		+			+
4	+	+	+		+		+	+	+	+	+	+	+	+	+	+	+		+	+
5																				
6	+	+	+		+		+	+	+	+	+	+	+	+	+	+	+		+	+
7	+	+	+		+			+	+	+	+	+	+	+	+	+	+		+	+
8																				
9																				
10					+		+	+	+		+	+		+	+		+			+
11																				
12																				
13					+		+	+	+		+	+		+	+		+			+
14																				
15																				
16					+		+	+	+		+	+		+	+		+			+
17																				
18	+	+	+		+		+	+	+	+	+	+	+	+	+	+	+		+	+
19					+		+	+	+		+	+		+	+		+			+
20																				

By tabulating Landsteiner's classification in a more convenient form, we get the following statement of it:

Group A. Serum agglutinates corpuscles of Group B.
Corpuscles agglutinated by serum of Groups B and C.

Group B. Serum agglutinates corpuscles of Group A.
Corpuscles agglutinated by serum of Groups A and C.

Group C. Serum agglutinates corpuscles of Groups A and B.
Corpuscles not agglutinated by serum of Groups A and B.

On examining the classification we see that the sera of all three groups are capable of agglutinating the corpuscles of some other group, that the corpuscles of Groups A and B are agglutinated by the sera of some other group, while it is not stated that the corpuscles of Group C are agglutinated by any serum. This gives one a starting point for the application of the classification.

In the series shown in Table IV we see that the corpuscles of a certain number of individuals have not been agglutinated by any serum. These individuals clearly cannot be placed in Group A or B because the corpuscles of the members of these groups are agglutinated. They may then belong in Group C, since it is not stated that the corpuscles of the members of this group are agglutinated at all.

One may then provisionally place in Group C all those members of the series whose corpuscles are not agglutinated at all. The remaining members of the series would then fall in Groups A and B. Thus we have:

Group C = 5, 8, 9, 11, 12, 14, 15, 17, 20.
Groups A and B = 1, 2, 3, 4, 6, 7, 10, 13, 16, 18, 19.

If we look at Table IV, we will see that the sera of all those whom we have placed in Group C do agglutinate the corpuscles of all those in Groups A and B, thus fulfilling the requirement for this group.

We have now to separate Groups A and B, and since the relations which these two groups bear to each other, are reciprocal, and the relations they bear to Group C are identical, we can arbitrarily select any one of the combined Groups, A and B, and place it in Group A and by applying the requirements of the classification, we can separate the members of Group B. For example let us place No. 1 in Group A. The requirements are that the serum of No. 1 shall agglutinate the corpuscles of Group B, and by examining the action of serum No. 1 on the corpuscles of the rest of the members of the combined Groups A and B, we find that it agglutinates the corpuscles of Nos. 4, 6, 7, 18. Hence we will place 4, 6, 7, 18 in Group B. Now the remainder of the combined Groups A and B must, if the classification is correct, belong in Group A. Group A will then consist of Nos. 1, 2, 3, 11, 13, 16, 19. According to the classification, the sera of all of these should agglutinate the corpuscles of Group B, and the corpuscles of this group should be agglutinated by the sera of Groups B and C.

By referring to Table IV, we find that the first of these requirements is fulfilled; namely, that the sera of Group A shall agglutinate the corpuscles of Group B, and that the corpuscles are agglutinated by the sera of all of the members of Group C, but, when we come to the requirement that they shall also be agglutinated by the sera of Group B, we find that they are agglutinated by serum No. 7, but not by Nos. 4, 6, 18. The requirements for Group B are fulfilled, with the same exception, namely, that sera Nos. 4, 6, and 18 do not agglutinate the corpuscles of Group A.

In attempting to apply this classification to each of the five series of twenty individuals, exceptions were always encountered, hence, a classification was sought which would cover all cases and to which there would be no exceptions. I found that such a classification required a separation into four groups, and I propose the following to which I have found no exceptions in the last 1600 tests:

Group I. Sera agglutinate no corpuscles.
Corpuscles agglutinated by sera of Groups II, III, IV.

Group II. Sera agglutinate corpuscles of Groups I, III.
Corpuscles agglutinated by sera of Groups III, IV.

Group III. Sera agglutinate corpuscles of Groups I, II.
Corpuscles agglutinated by sera of Groups II, IV.

Group IV. Sera agglutinate corpuscles of Groups I, II, III.
Corpuscles agglutinated by no serum.

Applying this classification to Table IV, we get the following separation:

Group I = Nos. 4, 6, 18.
Group II = " 1, 2, 3, 10, 13, 16, 19.
Group III = " 7.
Group IV = " 5, 8, 9, 11, 12, 14, 15, 17, 20.

Of the 100 bloods tested in series of 20 each, there have been found:

10 belonging to Group I.
40 " " " II.
7 " " " III.
43 " " " IV.

From this it is probable that Group III is the rarest, with Group I but little less infrequent, while Groups II and IV are about equally common.

It has been suggested that isoagglutination and isohemolysis may present a possible danger in the transfusion of blood from one individual to another.

Reference to the classification indicates that so far as agglutination is concerned, it probably would be safe to transfuse between members of any one group; at least, we can say that agglutination outside the body does not take place when the serum of any member of a group is added to the corpuscles of another member of the same group. If agglutination does constitute a source of danger in transfusion, one can see that a risk is run if one undertakes to transfuse from any member of one group to any member of another group, and that the risk is a double one when transfusion takes place between Groups II and III, since then the serum of both donor and donee is capable of agglutinating the corpuscles of the other.

A word in anticipation of a subject to be dealt with when we come to consider isohemolysis may be added here. In transfusion, among other things, we have to deal with the action of the serum of one individual on the corpuscles of another individual in the presence of the second individual's serum, and the first individual's corpuscles. Consequently numerous tests have been made to see if this condition inhibits agglutination. So far it has not been found to do so.

Having shown that individuals can be divided into four groups, according to the ability of their serum to agglutinate the corpuscles of other individuals and according to the ability of their corpuscles to be agglutinated by the serum of other individuals, my next study was to determine, if possible, upon what these differences depend.

In this work I have accepted Ehrlich's theory as being correct. This theory, as applied to the agglutination of red blood cells, assumes that the corpuscles in order to be agglutinated must possess receptors which are capable of uniting with a body which may be present in some sera called an agglutinin. Cells thus united to agglutinin are attracted to each other, come together and cohere in clumps, giving rise to the familiar phenomenon of agglutination. Now, if there is only one kind of hemagglutinophilic receptor, and one kind of isohemagglutinin, the corpuscles of any individual possessing such receptors will be agglutinated by any serum containing such agglutinin. That this is not the case can readily be seen by reference to Table IV, in which, for example, corpuscles of individual No. 1 possess receptors, as is shown by the fact that they are agglutinated by the serum of Nos. 5, 7, 8, etc., moreover serum No. 2 contains agglutinin since it is able to agglutinate corpuscles Nos. 4, 6, 18, etc. But corpuscles No. 1 are not agglutinated by serum No. 2, hence, we have to assume that the receptors of corpuscles No. 1 do not have an affinity for the agglutinin contained in serum No. 2. In other words, either the receptors of corpuscles No. 1 differ from the receptors of corpuscles Nos. 4, 6, 18, etc., or the agglutinin contained in serum No. 2 differs from the agglutinin contained in sera Nos. 5, 7, 8, etc.

If we postulate different kinds of agglutinophilic receptors, it follows that we must postulate different kinds of agglutinins and vice versa. Landsteiner (loc. cit.) reached the conclusion from his results that there were at least two kinds of agglutinin present in the serum in his cases, the one in Group A, the other in Group B, and both in Group C. My results have led me to somewhat different conclusions, and therefore I wish to present the evidence which I have obtained. I shall designate the different kinds of receptors by the small letters a, b, c, etc., and the different kinds of agglutinins by the large letters A, B, C, etc., in which it is intended to indicate that an affinity exists between receptors and agglutinin of like letters. Now, what is it necessary to assume in order to account for the existence of the four groups into which I have divided individuals? There are two (perhaps more) possibilities which would account for the facts which we observe.

First Possibility.

Group I = 4, 6, 18.	Serum contains no agglutinin. Corpuscles possess Recep., a.	Agglutinated by sera of Groups II, III, IV.
Group II = 1, 2, 3, 10, 16, 19.	Serum contains agglutinin A and C. Corpuscles possess Recep., b.	Agglutinates corpuscles of Groups I, III. Agglutinated by sera of Groups III, IV.
Group III = 7.	Serum contains agglutinin A and B. Corpuscles possess Recep., c.	Agglutinates corpuscles of Groups I, II. Agglutinated by sera of Groups II, IV.
Group IV = 5, 8, 9, 11, 12, 13, 14, 15, 17, 20.	Serum contains agglutinin A, B and C. Corpuscles possess no Recep,	Agglutinates corpuscles of Groups I, II, III. Agglutinated by none.

Or Second Possibility.

Group I.	Serum contains no agglutinin. Corpuscles possess Recep., a, b and c.
Group II.	Serum contains agglutinin A. Corpuscles possess Recep., b and c.
Group III.	Serum contains agglutinin B. Corpuscles possess Recep., a and c.
Group IV.	Serum contains agglutinin C. Corpuscles possess no Recep.

The problem now is to determine which of these two possibilities represents the true state of affairs. If the first possibility, then the serum of Group IV after absorption with the corpuscles of Group I will still be able to agglutinate the corpuscles of Groups II, III. If the second possibility, then the serum of Group IV after absorption with the corpuscle of Group I will not be able to agglutinate the corpuscles of Groups II, III.

The following single example will serve as an illustration of tests carried out to decide this point. To 1 cc. of serum 5 (Group IV) was added 0.1 cc. of corpuscles 4 (Group I) and the mixture allowed to stand in the thermostat for 1 hour. At the end of this time the corpuscles were found to be agglutinated into a solid mass. The clear supernatant fluid was then pipetted off from this tube and the following tests made with it.

Supernatant fluid.	5% susp. Corps.	Agglutination after 2 hrs. at 37° C.
(1) 0.25 cc.	Gr. I: No. 4 0.25 cc.	0
(2) 0.25 cc.	Gr. II: No. 1 0.25 cc.	0
(3) 0.25 cc.	Gr. III: No. 7 0.25 cc.	0

Test No. 1 showed that all of the agglutinin for corpuscles of Group I had been removed, while tests 2 and 3 showed that all of the agglutinin for Groups II and III had also been removed, indicating that the second rather than the first possibility represents the actual conditions. Thinking that perhaps too large a quantity of corpuscles of Group I had been used for the absorption, and that they might have mechanically removed the agglutinin for the other two groups, the experiment was repeated, using varying amounts of corpuscles for absorption until an amount of corpuscles of Group I was obtained which did not quite remove all of the agglutinin for Group I. Under these conditions it was found that the agglutinin for Group II and III had been extracted to the same extent as that for Group I, thus further indicating the correctness of the second possibility. However, I wish to repeat these experiments a number of times to guard against the possibility of error before affirming that the explanation given is correct.

I have not yet been able to classify individuals according to the isolytic action of their blood as has been done in the case of the isoagglutinative action. That there is a relationship between isoagglutinins and isohemolysins seems likely although this relationship may not extend further than their possible dependence upon a common causative factor.

What this causative factor is, we do not know. Some investigators have advanced the theory that the resorption of blood or its disintegration products stimulate the production of isoagglutinins and isohemolysins in man. We know that there is a physiological blood destruction going on constantly, and that in various morbid states, non-bacterial as well as bacterial, there is a pathological blood destruction, but no satisfactory proof has been brought forward that man responds to the resorption of his own blood, or its disintegration products by the production of agglutinins or hemolysins. The animal experiments along this line have been negative except in the hands of one or two investigators. Ehrlich and Morgenroth, as previously stated, were able to produce immune isohemolysins by the injection of the blood of one goat into another goat, but not by injecting into a goat its own blood. Moreover, Halban (*Agglutinationsversuche mit mütterlichem und kindlichem Blute.* Wien. klin. Wchnschr., 1900, XIII, p. 545) showed that fetal blood taken from the cord at birth often contained isoagglutinins even in cases where the maternal blood was shown to contain no isoagglutinin. In such cases it would be hard to refer the presence of the isoagglutinin in the child's blood to the resorption of blood which had undergone destruction under pathological influences, and since the maternal blood contained no isoagglutinin, it could not have been derived from that source.

Without inquiring more closely into the ultimate causative factor upon which isoagglutinin and isohemolysin depend, the view which I have suggested that they may depend on a common causative factor is strengthened by the work of Ford and Halsey (Contributions to the Study of Hemagglutinins and Hemolysins. J. Med. Research, 1904, Vol. VI), who showed, contrary to certain other observers, that agglutinins and hemolysins could not be produced independently by the injection of the stroma of red blood corpuscles or hemoglobin alone. When hemoglobin-free stroma was injected into suitable animals, they found that both agglutinins and hemolysins were produced and that the same result followed the injection of pure hemoglobin.

In regard to the relationship existing between isoagglutinins and isohemolysins, I may say that agglutination frequently occurs independently of hemolysis, but that the inverse relation occurs, i. e., hemolysis without the simultaneous or preceding occurrence of agglutination seems less likely. In my first experiments hemolysis without agglutination was frequently recorded, but closer attention to this point in subsequent experiments led me to doubt the correctness of these earlier observations.

Agglutination is a phenomenon which concerns the corpuscle as a whole, while hemolysis is a phenomenon which destroys the integrity of the corpuscle, and it is possible that agglutination cannot persist among corpuscles which have been damaged by the action of hemolysins. As a rule, however, agglutination proceeds more rapidly than does hemolysis and by observing the action of a serum, which contains both agglutinin and hemolysin, on susceptible corpuscles, one frequently sees agglutination set in which is subsequently broken up as hemolysis takes place; so that if the observations are not made until the lapse of 2 hours, in a case where the hemolysin is not quite sufficient to dissolve completely all of the corpuscles present, we may get the appearance of hemolysis having taken place without agglutination. As indicated in Tables II and III the occurrence of isoagglutinins in man is much more frequent than the occurrence of isohemolysins. In 100 individuals tested, 61 of whom were healthy and 39 suffering from various diseases isoagglutinins were found in 92 cases and isohemolysins in 25 cases. The latter, isohemolysins, have not been found in Group I, that is in those individuals whose serum contains no agglutinin, but have been found in each of the other three groups, Groups II, III, and IV. Moreover the same statement apparently applies to isohemolysins as was made in regard to isoagglutinins; namely, that the serum of any individual of one group may hemolyse the corpuscles of another individual in any other group except Group IV, but not the corpuscles of a member of same group.

In the hundred individuals tested in groups of 20, I have found only two exceptions to this rule, and it seems likely that the hemolysis in these two cases may have been due to accidental causes. A further point of considerable theoretical interest and of practical importance in its bearing on the question of transfusion in man was discovered.

Given an individual, A, whose serum is capable of hemolysing the corpuscles of another individual, B, in the test tube,

the hemolysis is prevented if the serum of B is added to the serum of A before it is allowed to act on the corpuscles B. For this experiment it is best to mix the two sera and allow them to remain in the thermostat for half an hour before adding the corpuscles, but even when the corpuscles are added immediately the inhibition is partial if not complete.

It was further found that the serum of any member of the same group as that to which the individual furnishing the corpuscles belonged would also exert an inhibiting action. Ascoli (*Isoagglutinine und Isolysine menschlicher Blutsera.* Münch. Med. Wchnschr., 1901, Vol. 48, No. 31, p. 1239) was able to show in a certain number of cases that the isolytic action was due to two bodies, one thermostable (amboceptor) the other thermolabile (complement). This he proved by the usual method of heating hemolytic serum to 56° C. for 20 minutes, and showing that it had lost its ability to cause solution of the red blood corpuscles, but that this power could be restored by the addition of the fresh serum of another individual, which serum alone was incapable of producing any hemolysis. Ascoli states that in a certain number of cases he was able to accomplish this reactivation, but in others the reactivation failed for reasons which remained to him inexplicable. I have confirmed Ascoli's statements regarding the amboceptor-complement nature of isohemolysin and of their relations to heat and in the light of the statements I have just made, it seems probable that in the cases where Ascoli was unable to reactivate his hemolytic sera after heating, that he may have been using for the reactivating serum, the blood of an individual belonging to the same group as the individual from whom the corpuscles were taken and that the reactivation failed, not through any lack of complement, but on account of the presence of inhibiting bodies in such a serum. In order to reactivate a given hemolytic serum one may best employ the serum (nonhemolytic) of a member of the same group as that to which the hemolytic serum belongs.

I have tested this property of the serum to inhibit the hemolysis of the homologous corpuscles, or the corpuscles of any member of the same group and found that it resists heating to 57° C. for half an hour, and is therefore thermostable.

I have next attempted to discover the point of action of this inhibiting body. Theoretically such a body might act by combining with, 1, the receptor group of the cells; 2, the cytophilic group of the amboceptor; 3, the complementophilic group of the amboceptor; 4, with the complement.

The first possibility, blocking of the receptor of the cell, can be ruled out at once, for if this occurred, cells first treated with the inhibiting serum and then removed by centrifugalization and washed would not be dissolved on the subsequent addition of a hemolytic serum. We know that the serum of any individual protects its own corpuscles from hemolysis by any other serum, but as soon as the corpuscles are removed from their own serum they may be dissolved by other hemolytic sera, showing that their receptors are free.

To determine which if either group of the amboceptor has been blocked, that is if the antihemolysin is an antiamboceptor, we may proceed as follows: To susceptible corpuscles add inactivated hemolytic serum and inactivated protective serum. After these have stood together for a while in the thermostat remove the corpuscles and wash them. Now if the cytophilic group of the amboceptor has been blocked the receptor group of the corpuscles will remain free, and they may be hemolyzed by the addition of fresh hemolytic serum, but not on the addition of complement alone; but if the complementophilic group of the amboceptor has been blocked the cells may have anchored the amboceptor-antiamboceptor combination and hence will not be hemolyzed on the addition even of fresh hemolytic serum. If the inhibiting body is an anticomplement, the cells after removal and washing should be hemolyzed on the addition of complement alone. In order to determine this point I selected an individual C from Group IV whose serum was hemolytic for the corpuscles of an individual A of Group I. Equal quantities of C's serum and A's serum were inactivated and added to A's corpuscles. After the mixture had stood for an hour in the thermostat at 37.5° C. the corpuscles were removed by centrifugalization, washed, suspended in a small amount of salt solution and to one portion complement alone was added (serum D, Gr. IV which had been shown to possess no hemolysin), and to another portion of the corpuscles fresh serum from C was added. Those corpuscles to which complement alone was added were not affected while those to which hemolysin was added underwent prompt solution showing that the antihemolysin is an antiamboceptor which acts by blocking the cytophilic group of the amboceptor.

At present I am only prepared to speculate as to the origin and nature of this antihemolysin.

Müller (*Ueber die Erzeugung hämolytischer Amboceptoren durch Seruminjection.* Münch. med. Wchnschr., 1902, XLIX, No. 32, p. 1330) refers to the work of Morgenroth in which he showed that by the injection of serum one could call forth the production of hemolytic amboceptors which are identical with those resulting from the injection of blood. Müller refers to his own earlier work in which he showed that a whole series of normal sera possess antihemolytic properties directed against the hemolysins contained in other normal sera. He proceeded to inject sera containing antihemolysin in an effort to produce an anti-antihemolysin, and thought at first that he had succeeded in accomplishing this, but closer scrutiny showed that he had merely produced a hemolytic serum. By injecting guinea-pig serum into another animal he obtained a serum capable of dissolving guinea-pig corpuscles. His explanation of the fact that the injection of serum alone is able to produce an hemolysin is that the serum must contain groups identical with the receptor groups of the corpuscles, and he further suggests that if the serum contains groups identical with the receptor groups of the corpuscles, such a serum should be able to bind the hemolysin and thus protect the corpuscles from hemolysis. I arrived at the same conclusion regarding the nature of the antihemolysin directed against isohemolysin which I observed.

Conclusions.

1. Isoagglutinins occur in the serum of about 90 per cent, and isohemolysins in about 25 per cent, of adult human beings.

2. These bodies appear with approximately the same relative frequency in health and in various diseases and therefore have no diagnostic significance.

3. In a number of healthy individuals whose blood was repeatedly tested at varying intervals of time the agglutinating action was found not to vary, while in some cases the hemolytic action which was present in earlier tests was absent in subsequent tests.

4. There are at least three different isoagglutinins and three isohemolysins in human sera and three different isoagglutinophilic and three isohemolysinophilic receptors possessed by human red blood corpuscles.

5. There are human sera which contain no isoagglutinin and isohemolysin but whose corpuscles possess receptors for isoagglutinin and isohemolysin.

6. No individual serum which I have investigated appears to contain more than one of the three kinds of isoagglutinin or isohemolysin.

7. The corpuscles of a given individual may possess no isoagglutinophilic or isohemolysinophilic receptors or they may possess two, or all three kinds of these receptors.

8. Human beings can be divided into four groups according to the ability of their serum to cause isoagglutination and of their corpuscles to be isoagglutinated.

9. The serum of members of any one group will not agglutinate or hemolyse the corpuscles of other members of the same group but will agglutinate and may hemolyse the corpuscles of members of any other group except those of Group IV. This may have a practical application in the transfusion of blood from one individual to another.

10. Autoagglutination was not observed in any of the 213 cases investigated and autohemolysis was observed only once. In the latter case the hemolysis may have been due to extraneous causes.

11. A strict classification of individuals according to the isohemolytic action of the blood has not been accomplished.

12. Isoagglutination may occur independently of isohemolysis but isohemolysis is probably always preceded or accompanied by isoagglutination.

13. All the sera investigated contained an antihemolysin which protected the homologous corpuscles and those of members of the same group from solution by any other serum.

14. This antihemolysin is an antiamboceptor which acts by uniting with the cytophilic group of the hemolysin thus blocking it off from the red blood cell; and probably consists of receptor groups of the red blood cells which have been cast off from the cells or set free by the physiological or pathological destruction of the corpuscles.

15. Isoagglutinin is thermostable; that is it resists heating to 55° C. for 30 minutes.

16. Isohemolysin consists of two components; one, thermostable, resisting heating to 55° C. for 30 minutes (amboceptor), the other thermolabile, destroyed by heating to 55° C. for 30 minutes (complement).

17. The antihemolysin is thermostable, resisting heating to 55° C. for 30 minutes.

18. Any non-lytic serum may be used to reactivate an inactivated hemolytic serum provided the reactivating serum does not contain antihemolysin against the amboceptor of the hemolytic serum. In other words the reactivating serum must not be chosen from the same group as that to which the corpuscles to be hemolyzed belong. The reactivating serum may best be chosen from the same group as that to which the hemolytic serum belongs.

19. The origin of isoagglutinin and isohemolysin has not yet been satisfactorily determined. It probably cannot be referred to the destruction and resorption by an individual of his own blood.

Note.—Since the above paper went to press there has come to my notice in the *Jahresbericht für Neurologie und Psychiatrie*, 1907, the review of a paper by Jan. Janský, entitled "Haematologische Studien bei Psychotikern," *Klinický Sbornik*, No. 2, 1907; in which the author divides individuals into four groups according to the agglutinating reaction of the blood quite in the same way that I have done, except that his Group I corresponds to my Group IV and *vice versa*.

Had this paper come to my notice in time I could have given the author credit in the body of my paper for his priority in establishing the correct classification.

CLINICAL EXPERIENCE WITH THE WASSERMANN REACTION IN THE JOHNS HOPKINS HOSPITAL.

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I.

The great importance of an accurate method for the diagnosis of syphilis in its obscure forms is a matter of general recognition. Though in the strictest sense a constitutional disease, a definite diagnosis has hitherto been impossible in a considerable number of cases which did not happen to show some cutaneous or other external manifestation. Hence the announcement by Wassermann of the discovery of a reliable method of serum diagnosis aroused unusual interest and led to a very large amount of confirmatory work.

As originally devised by Wassermann in 1906,[1] the test depended on the principle of complement fixation formulated

by Bordet and Gengou in 1901.[2] They found that if a bacterial culture was added to the fresh blood serum of an animal immunized to that organism, the complement present in the serum would be removed, or fixed, so that it would no longer be able to dissolve sensitized red blood corpuscles.

If a rabbit is injected with the red blood corpuscles of a sheep, the blood serum of the rabbit will acquire the power of dissolving the sheep's corpuscles. This power of dissolving the sheep corpuscles is not present in normal rabbit serum, but only in that of the treated animal. It is specific. That is, it is effective only in dissolving the corpuscles of that one species of animal, the sheep. It will not dissolve those, for example, of the ox, the dog, or the chicken. In order to carry out this solution, the rabbit serum must be fresh. If it is old, or if heated to 56° C. for 20 minutes, it will lose this power, but will regain it if a little fresh serum is added from any normal animal, as e. g. from a guinea-pig. Such a solution, then, depends on the presence of two substances. One, not present in normal rabbits, but formed as a result of the injection of sheep corpuscles, is called the amboceptor, immune body, or hæmolysin. It is specific, and since it is not destroyed by heating, is said to be thermostabile. The serum containing it is known as an hæmolytic serum. The second, present in all sera, and destroyed by heating, is called complement. Corpuscles which have been mixed with an inactivated specific hæmolytic serum, such as the rabbit serum just described, are said to be sensitized; they are so changed as to be dissolved on the addition of free complement. For the purposes of this reaction, they may be regarded simply as a reagent for the detection of free complement in a solution, hæmolysis occurring, if free complement is present.

Any substance, bacterial or otherwise, which on injection into an animal, results in the production of specific antibodies is known as an antigen.

Bordet and Gengou showed that if an emulsion of typhoid bacilli (an antigen) is added to the fresh serum of an animal immunized to typhoid (and containing specific antibodies), the serum would lose its power of dissolving sensitized corpuscles, due to the removal or fixation of its complement. They found this phenomenon to be specific. If any serum was used except one immune to the particular organism with whose culture it was mixed, the complement would not be disturbed and the serum would retain its power of dissolving the sensitized corpuscles. They devised the test for detecting and identifying specific antibodies in immunized animals; and applied it in a few cases to man.

Wassermann conceived the idea of applying this principle to the diagnosis of syphilis. As an antigen he substituted for the bacterial emulsion an aqueous extract of the liver of a syphilitic fetus. He found that the addition of a small amount of such an extract to the inactivated serum of a syphilitic patient, to which free complement had been added, would fix the complement present. If sensitized red corpuscles were added, no hæmolysis would occur. If a normal or non-syphilitic serum were used, the complement would remain free, and the corpuscles would be dissolved. He tested the reaction on infected apes, and also clinically on man, and obtained results so constant as to give promise of great practical value.

Subsequent work by a great many investigators has confirmed his views as to its clinical value, non-syphilitic sera rarely giving a positive reaction. But the prevailing ideas as to the nature of the reaction have been materially changed. It was soon shown by Marie and Levaditi,[3] Weil and Braun,[4] Levaditi and Yamanouchi,[5] and others that in larger quantities, extracts of normal human livers, human or guinea-pig hearts, and of some other tissues, would also fix complement when combined with syphilitic sera. The antigenic substances in the syphilitic liver extracts could not be specific, in the strict sense, not being derived from the syphilitic organism or its by-products in the affected organs, but were substances present in normal organs, occurring in the syphilitic organs in increased amounts.

It was then shown by Landsteiner, Mueller and Pötzel[6] that an alcoholic liver extract was (nearly) as efficient an antigen as an aqueous extract. Such an extract contains no complex albuminous substances such as had been supposed were concerned in the reaction, but relatively simple fatty substances known as lipoids, such as lecithin, cholesterin, and sodium oleate. It has since been shown that lecithin, and some of the others, in solution will fix complement when combined with syphilitic sera. The reaction cannot be considered biologically specific, in the sense of a combination between a specific bacterial substance and an immune body, but merely as one that has been shown empirically to be characteristic of syphilis. The exact mechanism of the reaction is not understood, but it can hardly be a specific immunity reaction, as was originally supposed.

The technique of the reaction is somewhat complicated.[7, 8, 9] None of the simplified methods that have been sufficiently tested have proved as reliable as the original method, which was employed in the present series, except that in most cases one-fourth of the quantity of each constituent was used.

The blood of the patient was obtained as a rule, from the median basilic vein, with a small aspirating syringe. If carefully done with a small, sharp needle, it causes practically no discomfort, and is entirely without danger. The test was usually made the day the blood was obtained; in some cases on the following day. If the serum is sterile, and kept on ice, there does not seem to be much weakening of the reaction within a week. Serum that is visibly contaminated is unfit for use. After the serum has separated, it is inactivated by heating it in a small sealed tube, in a water bath, to 56° C. for 20 minutes. This not only destroys the complement present, but also weakens the reacting power of the serum. This seems necessary, as positive reactions have been reported in non-syphilitic sera which had not been heated.[10, 11] This has been confirmed in the present series of cases, several of which gave negative reactions after inactivation, but showed strong, or even complete fixation of complement when fresh. In a few cases the reverse is true, probably on account of the additional complement present in the patient's serum.

As antigen was used an alcoholic extract of a syphilitic fetal liver, in which the presence of spirochætæ had been demonstrated in sections by Levaditi's method. Where quantitative comparative tests have been made with different antigens, it has been shown [12, 13, 14] that syphilitic liver extracts are most satisfactory. They give positive reactions with syphilitic sera in greater dilution, and have less independent anti-complementary power, measured by the amount of extract which will inhibit hæmolysis, in the absence of any patient's serum. The activity of such extracts is quite independent of the occurrence or number of spirochætæ present. The best substitute is an alcoholic extract of normal human or guinea-pig heart muscle. Lecithin solutions are least satisfactory. Aqueous extracts of syphilitic fetal livers are more efficient than alcoholic in giving a somewhat larger percentage of positive reactions with syphilitic sera; but they are more variable, and much more unstable. The extract is made by grinding up the liver, shaking it for several hours with ten volumes of absolute alcohol, and filtering. It will keep indefinitely.

There is considerable variation in the behavior of different extracts to syphilitic sera of weak reacting power. Such sera may give a positive reaction with one extract, and a negative with another. Properly controlled, fixation with any extract that is known to be reliable may be accepted as a positive reaction.

As complement, fresh guinea-pig serum is used in 1 to 10 dilution. It was used 12 to 18 hours after bleeding. Small amounts may be aspirated directly from the heart, without injury to the animal if this be done under ether.

As a hæmolytic serum is used the serum of a rabbit immunized to sheep corpuscles. The rabbit is given intraperitoneal injections of washed corpuscles at 5-day intervals, in doses increasing from 2 to 10 cc. After 6 doses the animal is left for 10 days without further treatment. A small amount of blood is then withdrawn and tested. If active in a dilution of 1 to 1000 or higher, it is best to bleed the anesthetized rabbit to death. The serum is put in sealed tubes, inactivated and kept on ice. Thus preserved, it will lose but little strength within 3 or 4 months. In the living animal, the strength of the serum varies greatly from day to day.

The sheep's blood is obtained by aspiration from the jugular vein. It is mixed at once with 1.5 per cent sodium citrate in .85 per cent salt solution to prevent clotting. The corpuscles are removed by centrifugalization, are washed four times in salt solution to remove all trace of sheep serum, are centrifugalized to constant volume, and a 5 per cent suspension is made in salt solution.

The smallest quantity of rabbit serum that is necessary to dissolve 1 cc. of a 5 per cent suspension of sheep corpuscles in the presence of 0.1 cc. fresh guinea-pig serum is determined, and three times this amount is used in the final tests.

To 0.2 cc. of inactivated patient's serum are added 0.1 cc. guinea-pig serum, as complement, and 0.1 cc. of liver extract, each fraction being first diluted up to 1 cc. The mixture is placed in the thermostat 1 hour to enable complement fixation to occur. There is then added 1 cc. of diluted rabbit serum, the strength of which has been previously determined; and 1 cc. of a 5 per cent suspension of sheep corpuscles. The mixture is again placed in the thermostat for 2 hours, shaking gently several times during the incubation. The tubes are kept on ice over night and then read. In positive cases, where complement fixation has occurred, the corpuscles are not dissolved. In the negative cases they are completely dissolved.

Each step in the process must be carefully controlled. The serum of each patient, as well as the liver extract must be tested independently in double the quantity used in the final test, without giving any fixation of complement. The serum of a normal or non-syphilitic case must always be tested as a control, and must show complete hæmolysis. Partial fixation may be considered as indicating a positive reaction, provided the degree of hæmolysis is slight, and all the control tubes show complete hæmolysis. Border line cases occur where the result is in doubt. Such cases should be repeated, using if possible a different antigen solution.

Although there is nothing in the test that is technically difficult, or that requires any special skill, some experience and a uniform technique are required to insure reliable and comparable results. For example, even the manner and rapidity with which an alcoholic antigen solution is diluted may influence the result of the reaction.[11] The reliability of the results depends chiefly on the care with which each step in the process is carried out.

Aside from the difficulties in technique, there is one inherent defect in the test that has been especially emphasized by Noguchi.[15] Normal human serum contains amboceptors (hæmolysin) for sheep corpuscles, in amounts varying from a mere trace up to several times the quantity needed for the test. Hence if, in a given case, the human serum to be tested is strongly hæmolytic, the addition of the usual 2 or 3 units of hæmolytic rabbit serum may result in a large excess of hæmolysin being present. This may cause complete hæmolysis in positive cases where a small amount of complement remains free, or may even to some extent liberate complement which has been fixed. Hence a few positive reactions will be missed. An attempt was made by Bauer [16] to avoid this difficulty, but no better results were obtained than by the original method.

Noguchi has recently [15] proposed a new method which not only attempts to overcome this difficulty, but greatly simplifies the technique of the reaction. He uses the serum of a rabbit that is immunized to human corpuscles. Human serum, at the degree of dilution used in the test, does not contain hæmolysin, in any appreciable amount, for human corpuscles. He also thinks it unnecessary to inactivate the sera. He reports a larger percentage of positive reactions in certain and doubtful cases than by the original method, and in cases in which this was negative, showed that the serum in question contained an excess of amboceptors for sheep cor-

puscles. He has tried to make it more generally applicable by drying on bits of filter paper the antigen solution and the hæmolytic serum, each in quantities suitable for a single test. It promises to be a very important and practical simplification of the reaction. In a limited number of cases in which it was tried here, using papers very kindly furnished by Noguchi, fairly satisfactory results were obtained.

The results that have been reported are about as follows:[7, 17] In primary syphilis from 50 to 60 per cent give a positive reaction. In active secondary and tertiary syphilis, 80 per cent or more are positive. In latent syphilis about 40 per cent are positivc. In congenital syphilis[18] 90 to 100 per cent are positive.

Cases of tabes and general paresis also give a positive reaction, both in the spinal fluid and the blood serum; tabes in 50 to 60 per cent; general paresis in 90 to 100 per cent.[17, 18, 19, 20] Patients giving no history of syphilis seem nearly as likely to give a positive reaction as those who admit an infection. The smaller percentage in tabes is possibly to be attributed to the slower course of the disease, and the longer interval since the syphilitic infection. In view of the nonspecificity of the reaction, it can hardly be accepted as final proof of the pre-existence of syphilis in all such cases.

A few conditions have been reported giving a positive reaction where syphilis could apparently be excluded. The most important one is scarlet fever.[18, 21] During the fever and for a few weeks after it a positive reaction is not infrequent. Positive reactions have been reported in a number of cases of leprosy,[22] in framboesia,[23] and in animals infected with trypanosomes. Isolated cases have been reported in a variety of other conditions,[24] but are so exceptional as to be open to suspicion, and detract nothing from the reliability of the reaction.

The results obtained in this clinic are quite in harmony with those reported elsewhere. No effort has been made to include many cases of manifest syphilis, but rather to select cases where the diagnosis was in doubt. The reaction was also tried in a variety of other conditions in which syphilis could be excluded.

Out of 268 cases in this series which have been studied, which Professor Barker has kindly permitted me to publish, in 99 there was nothing in the history, symptoms, or physical signs to suggest syphilis. All gave negative reactions. Some were normal or nearly normal persons. Most of them, however, were patients with serious acute or chronic disease. Among them may be mentioned: acute and chronic urethritis, pneumonia (6 cases), typhoid fever (5 cases), pulmonary tuberculosis (3 cases), miliary tuberculosis (2 cases), tuberculous meningitis (5 cases), chronic osteomyelitis, acute rheumatic fever with endocarditis, arteriosclerosis, myocarditis, and chronic nephritis (7 cases), diabetes (2 cases), arthritis deformans, advanced carcinoma (9 cases), alcoholic cirrhosis (5 cases), hæmochromatosis, Hodgkin's disease, pernicious anæmia, congenital icterus, peripheral neuritis, multiple sclerosis (3 cases), progressive central muscular atrophy, syringomyelia (2 cases), paralysis agitans (4 cases).

Of 45 cases clinically syphilitic, 33, or 73 per cent gave positive reactions. Of 5 cases of primary syphilis, 4, or 80 per cent were positive. Of 13 cases of secondary syphilis, 9, or 70 per cent were positive. Three of the 4 negative cases had received thorough treatment. Of 19 cases of tertiary syphilis with definite lesions, 16, or 84 per cent were positive.

Two of these patients showed tumors of the chest wall, clinically somewhat resembling sarcomata. In each the result of the (positive) reaction was confirmed by an exploratory incision and microscopical examination. A third patient with pulmonary tuberculosis had an ulcer on the back of the forearm of a year's duration, which for a time was believed to be tuberculous. Although he denied syphilis, suspicion as to its character finally arose. He gave a positive reaction. The ulcer healed rapidly under antisyphilitic treatment.

Of 101 cases in which the diagnosis was in doubt, 37 gave a positive reaction. In 50 of these cases clinically syphilis seems probable. Positive reactions were obtained in 33, or 66 per cent. In 51 cases in which without the reaction, syphilis would seem unlikely, 4 gave positive reactions. In none could syphilis be excluded.

Positive reactions were obtained in 2 other cases giving no history of syphilis, and presenting as their chief sign of infection a well marked general glandular enlargement.

In the series, 34 cases were found who gave a definite history of an old syphilis that could be accurately dated, varying from 4 to 45 years before examination. In 13 of these there was nothing definite to indicate an active process. Of the 13, 10 gave a negative reaction. The interval between the infection and the examination varied from 11 to 45 years, and averaged 24 years. A positive reaction was obtained in 3. One, a man of 35, was suffering from adherent pericardium, with broken compensation. He gave a definite history of syphilis 16 years before, but showed no signs of the disease except a few old scars on the shins. A second case, a man of 40, with amœbic dysentery, gave a history of infection 15 years before. He showed the scar of the primary lesion, and a slight general glandular enlargement. The third case was a colored sailor of 26, with acute lobar pneumonia. He had a primary lesion at 20. He also showed a scar, and a general glandular enlargement.

Of the 21 cases showing some sign of active disease, positive reactions were obtained in 12, and negative in 9. Of the 9 negative cases, 5 were tabetics, who gave a history of infection from 8 to 26 years before. One with an aortic aneurysm was infected 30 years before; 1 with a rectal stricture 33 years before; 1 with tertiary ulcers, 7 years before; 1 with cerebral symptoms 4 years before. Of the 12 active cases giving positive reactions, 3 were cases of tabes whose infection dated back 9, 10 and 30 years respectively. Three were cases of aortic aneurysm, 2 of aortic insufficiency, and 4 of tertiary syphilis with gummata. The interval since infection varied from 8 to 39 years, and averaged 19 years. Only 1 had had symptoms referable to syphilis in the interval.

Of special interest are the cases with vascular lesions. Of 20 cases of aortic aneurysm tested, 10, or 50 per cent,

gave positive reactions. Only 4 of the 10 gave a history of syphilis. Two of the others who gave positive reactions came to autopsy, and showed a localized productive mesaortitis, such as is usually considered characteristic of syphilis. In 9 other cases showing arteriosclerosis and aortic insufficiency, but no indications of aneurysm, 6 gave positive reactions. Only 3 of the 6 gave a history of syphilis.

In 6 cases giving clinical signs of cerebral syphilis, 3 positive reactions were obtained. One of the negative cases had received thorough treatment.

Among other cases in which the reaction was of importance in reaching a diagnosis may be mentioned a case of syphilitic cirrhosis; a case of bilateral synovitis of the knees with no other definite signs; a case of tumor of the spleen; and a case of obliterative endarteritis with gangrene of the leg.

It must be borne in mind that syphilis may coexist with other diseases. Thus, a colored man, 29 years old, came into the hospital with signs of intracranial tumor. He gave a suspicious history, and physical signs pointed to syphilis, which was confirmed by a positive reaction. At operation it was found that his serious symptoms were not due to syphilis, but to a cerebral abscess containing streptococci.

Of 15 cases of tabes tested, 6, or 40 per cent, gave a positive reaction. Of the 9 negative cases, 4 had recently received vigorous mercurial treatment. Eleven of the 15 gave a history of syphilis, and 5 of these gave positive reactions. Of the 4 who denied infection, 1 gave a positive reaction. In 5 the reaction was tested in both blood and spinal fluid. In 2 negative reactions were obtained in both; in 1, positive in both. In 1 the blood was positive and the spinal fluid negative. In 1, the spinal fluid only was positive.

In 7 cases of general paresis, positive reactions were obtained in all. All but 1 of these patients gave a history of syphilis. In 4 cases both blood and spinal fluid were positive, the blood giving the reaction in a higher dilution than the spinal fluid. In 2 the blood only was positive. In 1 the blood gave a negative reaction, but the spinal fluid a positive. I am indebted for these specimens to the staff of the Sheppard and Enoch Pratt Hospital, who kindly placed them at my disposal.

Mercurial treatment tends to weaken the reaction. But disappearance of the reaction does not mean cure. Such cases are still liable to relapse, although much less so than those cases in which a positive reaction persists in spite of treatment.[25] A positive reaction is considered by many as in itself an indication for treatment. But it is not certain that this is always the case. Instances have been cited of positive reactions in patients some years after all signs and symptoms had apparently disappeared. Such cases would have to be followed for a very long period before the presence of some latent lesion, of a developing aneurysm, or parasyphilitic affection could be excluded.

The reaction is unreliable for prognostic purposes. Mild cases yielding readily to treatment may react as strongly as severe, intractable ones. The reverse, however, is undoubtedly the rule.

In estimating the diagnostic value of the reaction, it must constantly be borne in mind that very little reliance can be placed in a negative reaction. Not infrequently a negative reaction is obtained in a patient with active secondary or tertiary lesions. In this respect its limitations are analogous to those of the Widal reaction in typhoid fever.

It is safest to regard a positive reaction as simply indicating a pre-existing infection. Though usually an active one, it may be latent, and not the cause of the symptoms present. While it may be going too far to accept a positive reaction as absolute proof of syphilis, if the exceptions noted are kept in mind, it may be considered conclusive for all practical purposes. In view of the extensive, almost unanimous confirmation it has received, the test must be regarded as a clinical method of very great reliability.

Summary.

In 99 cases where syphilis could be excluded the reaction was negative in all. In 51 doubtful cases in which clinically syphilis was not probable, the reaction was positive in 4; in 50 in which syphilis was probable, a positive reaction was obtained in 33, or 66 per cent. In 45 cases which were certainly syphilitic, a positive reaction was obtained in 33, or 73 per cent. Excluding cases which had recently received thorough mercurial treatment, positive reactions were obtained in about 82 per cent of the cases showing active syphilitic lesions. Positive reactions were obtained in 40 per cent of 15 cases of tabes, and in all of the 7 cases of general paresis which were tested.

Note.—Since the paper was submitted for publication several reports have appeared which in the main support Noguchi's claims as to the reliability of his method. However, until it has been more thoroughly controlled by experienced workers in other laboratories, results obtained with it should still be accepted with some caution, especially if the sera tested are not inactivated. It will certainly not yield reliable results in inexperienced hands.

The more recent work also indicates that the reaction affords a valuable (though not absolute) indication for treatment. With few exceptions, every patient giving a positive reaction should receive treatment with mercury until the reaction becomes permanently negative.

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ETIOLOGY OF MOVABLE KIDNEY.

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It is surprising that a condition so common and so easy of detection as movable kidney should have been for so long absolutely unknown. Nowhere in the references to Hippocrates, Galen, Paul of Aegina, or Avicenna do we find anything to indicate that they were acquainted with this abnormality. Many of the renal affections were recognized by the older writers and treated in a manner which seems rational to us to-day. Hydronephrosis, so frequently the result of a movable kidney, was described by Galen under the term Ischuria. But to Franciscus de Pedemontio, who lived the latter part of the fifteenth century, must be given the credit of being the first to call attention to the simple, uncomplicated movable kidney. Apparently, he did not lay much stress upon his discovery, and regarded it merely as an interesting anatomical curiosity with little or no clinical importance.

Not until the time of Riolan, in the middle of the seventeenth century, do we find any description of the clinical manifestations of movable kidney, known then as "dislocation of the kidney." Riolan (Encheiridium anatomicum et pethologicum, Lugd. Batav., 1649) has expressed so clearly and unmistakably his views of movable kidney that I would quote from him the following description:

> Although the kidneys are firmly attached to the loins by the glue of the fat, yet sometimes they become loose and fall forwards; sometimes they slip down to the hypogastrium—not without danger to life; this is so true that it is by no means to be doubted. This happens especially, not only because of the fat in which they are wrapped liquefying, but also from their weight, when they are so large, from tumor or stone enclosed in their cavities that they cannot be held by their own fastenings in their own places, and then, for a while, they stop there, but at length rot and suffer an abscess.

Even to-day, the absorption of the fat in the capsule of the kidney is considered an important etiological factor in nephroptosis.

For a century after Riolan's publication the medical profession made absolutely no advance in its knowledge of malposition of the kidney. The great Haller, who lived during the latter part of the eighteenth century, apparently did not know any more about movable kidney than was known by Riolan.

An abstract from the posthumous works of Matthew Baillie, the last of the celebrated holders of the gold-headed cane, indicates how much was known in regard to nephroptosis at the beginning of the nineteenth century. Baillie says:

> In four or five instances I have felt a loose tumor in the situation of one of the kidneys, which could easily be moved up and down with slight pressure from the hand. The tumor is of considerable firmness, and has a good deal the shape and size of the kidney. It is attended with very little uneasiness to the patient, and the general health is very little, if at all, affected by it. When felt in women it has been mistaken for an enlarged ovarium; but it has neither the shape of an enlarged ovarium, nor is it in the situation in which an enlarged ovarium is commonly found. I have not had an opportunity of examining this

disease in the dead body; I am therefore not certain about its nature, but I am rather disposed to think that it is a kidney more loosely attached than usual to the subjacent and surrounding parts.

In the Lancet, of 1836, there appeared an article by R. C. King describing an operation, which, although unsuccessful, was so far as I can discover the first attempt to cure a movable kidney by surgical means. King says as follows:

In March, 1834, Sophia Puttock, aged 40, complained of suffering very greatly from a variety of unpleasant feelings in her abdomen, back, and lower extremities. She spoke of herself as being rendered perfectly miserable and feeling her life a burden. On examining the abdomen, I perceived a tumor situated on the right side, about midway between the superior spine of the ileum and the edge of the ribs above it; the tumor appeared to be between 4 and 5 inches long, and 2 or 3 inches broad, forming in shape more or less of the segment of an oval. It was tender to the touch, and apparently attached by an extended medium. It could be moved with facility in all directions downward, and laterally, to an extent of 4 inches. It could be passed upwards in the direction of the liver until it seemed to disappear under its concavity; and when it was pressed upon in that direction it became lost to the touch, and did not descend without an alteration in the position of the person, but whenever an examination took place, in the first instance the tumor was always in its centrical position. I cannot say that I thought that the health of the person was particularly deranged, or much affected by the presence of the tumor, but there was a depression of feeling which rendered life so irksome as to create a disposition to submit to any treatment which might afford a prospect of relief. All the usual modes of treatment having been resorted to without benefit, I asked the patient if she was willing to have it removed. She embraced the suggestion with eagerness, and pressed me so much to make the attempt that I consented. Indeed, the night before the day fixed for the operation, she wrote to me, expressing a hope that I should not waver in my resolution, as her own determination was not in the least shaken. The case was examined by my friend, Mr. Jeaffreson, surgeon, of Framlingham, and he coincided in the opinion that an attempt to remove the tumor was justifiable, under existing circumstances. On the seventh of March, 1834, the operation took place in the presence of Mr. Jeaffreson, Mr. Lanchester, of Laxfield, and five other members of the profession. Previous to its performance they were asked, seriatim, to examine the patient, and give their opinions of the propriety of the attempt. They all agreed that the attempt was justifiable.

The patient was laid in a horizontal position, and a vertical incision was made through the parietes of the abdomen and linea semilunaris, to the extent of about 7 or 8 inches. On the cavity being thus exposed, the fingers were passed down to search for the tumor; it was not met with. To give greater facility for examination, the wound was enlarged in the direction of the lumbar vertebræ, for about 4 inches. The search was repeated most carefully, not only in the perpendicular direction, but upwards towards the liver and the small of the stomach. Several of the gentlemen present repeated the attempt to find the tumor, but unsuccessfully. The kidney of the same side was handled, and appeared to be more movable than natural, as it could be raised from its position nearly 2 inches. After the cavity of the abdomen had been exposed for about 20 minutes, it was determined to reclose it, which was done without difficulty, by the common interrupted suture.

The description of this operation by King would seem to indicate that the medical profession at that time was still a little hazy about the symptoms of movable kidney. It was, however, only seven years later (1841) when appeared that excellent work by Rayer, entitled "Traité des maladies des reins." I am sorry that time does not permit me to quote extensively from the work of Rayer, but I will at least give his views concerning the etiology of movable kidney, as it has a direct bearing upon the trend of this paper, and also coincides pretty well with the generally accepted views of the present day.

Rayer says:

The mobility of the kidneys constitutes a morbid state which has been little studied and which is much more frequent than is commonly thought. The right kidney is almost exclusively the seat of that anomaly; it is more frequent in women than in men. Often it occurs with an increase in the size of the liver, with a displacement of the intestine, or with a displacement of the uterus; it may also be the result of a particular arrangement of the peritoneum, from a deviation of the kidney, from a twisting of the vessels, etc. Multiple pregnancies, efforts to carry or to lift heavy objects, have appeared in some cases to be the cause of displacement of the right kidney, which in other cases could not be explained.

Since the time of Rayer, the literature which has accumulated upon all phases of movable kidney is tremendous, and I shall not attempt to review it in this paper. There have appeared, however, two monographs which especially interested me and which are directly responsible for the few investigations which I have made. The first, by Becher and Lenhoff, entitled, "Körperform und Lage der Nieren," appeared in the Deutsche medicinische Wochenschrift of August, 1898. The other by H. L. Harris, entitled "Movable Kidney—Its Cause and Treatment," appeared in the Journal of the American Medical Association, June 1, 1901. Becher and Lenhoff were impressed by the fact that the patients having movable or floating kidneys also had a fairly distinct type of chest and abdomen. The chest which they associated with movable kidney was long, narrow, and contracted at its lower end; or in other words, funnel-shaped, in contradistinction to the broad, cylindrical, well-developed chest. In 1901, Harris after examining a large number of cases came to the same conclusion as Becher and Lenhoff that the shape of the chest was the chief etiological factor of nephroptosis. The conclusions of Becher and Lenhoff and of Harris seemed to be so well founded that I was surprised to find that in the numerous articles appearing since 1901, very little reference was made to their work.

The deductions which I shall draw later are based upon the routine examination of 103 white women, 50 colored women, and 25 white men.

In each case I noted the age; occupation; any loss of weight, with cause; clothing, such as history of lacing, etc.; any previous injury; general appearance of the patient, whether well-nourished or emaciated; the condition of the abdominal wall, whether fat or thin, tense or relaxed; also examination of the pelvic structures; and finally, the following measurements: The distance from the suprasternal notch to the top of the symphysis pubis, circumference of the

lower part of the chest at the level of the seventh costal cartilage, circumference of the abdomen at the level of the umbilicus, circumference about the crest of the ilium, size of subcostal angle, and the distance from the crest of the ilium to the last rib. The measurements were taken with the patient flat on the back with no pillow under the head. The circular measurements were also taken at the end of normal expiration. The patients were always examined in both the supine and standing positions. By far the best method to detect a movable kidney is with the patient standing. To examine the right kidney, have her rest the right foot on some object about six inches high and lean a little to the right side. For the left kidney a corresponding position is assumed. This gives maximum muscular relaxation and full play to gravity.

I have not considered a kidney abnormally mobile unless half or more of the organ could be felt. In most cases if thorough relaxation is obtained and the patient is not too fat, the lower pole of the right kidney can be felt, so that it can hardly be considered abnormal.

The routine examination of seventy-five unselected cases of white women revealed movable kidney in sixteen, or 21.3 per cent. In some, only half of the kidney could be felt, while in others it could be displaced to the pelvis and opposite side of the abdomen. In fifty colored women there were four cases of movable kidney, or 8 per cent. Examination of twenty-five white men revealed only one movable kidney, or 4 per cent.

Nearly all of these women were patients in the gynecological dispensary, so that possibly the same number examined elsewhere might show somewhat different results. At the same time, I have examined on the wards and elsewhere thirty-four cases of movable or floating kidney, making in all, fifty cases. This would not be a very large number from which to draw conclusions, except for the fact that during the past three years, I have examined for movable kidney most of the patients that have fallen to my lot—between two and three thousand. And I find that the results gotten by examining carefully a smaller number of patients agree fairly accurately with results obtained by superficial examination of over two thousand cases.

Let us first consider briefly some of the generally accepted causes of movable kidney.

Pregnancy.—As movable kidney is so much more frequent in women than in men, it is natural when seeking a cause, that those functions peculiar to women should be considered of great etiological importance; and pregnancy, the function which causes such changes in the relation of the abdomen and pelvic viscera, was among the first to be held responsible for nephroptosis.

Landau, of Berlin, in 1881, made the following statement:

> The vast majority of women affected with movable kidney have borne many children, and, as shown by the appended table of my own observations, it is striking how frequently their deliveries had followed each other closely. Among the 42 cases observed by me only two are nulliparæ, and of these, one had carried a large ovarian tumor for 18 years and had acquired a pendulous belly after I had removed it.

It is hard to understand how Landau could have gathered such remarkable statistics, for we know now that movable kidney is quite common in nulliparæ.

The fifty cases of movable kidney which I recently examined showed the following results:

1	had	had	12	children.
1	"	"	10	"
1	"	"	9	"
2	"	"	8	"
1	"	"	7	"
1	"	"	6	"
3	"	"	5	"
2	"	"	4	"
4	"	"	3	"
11	"	"	2	"
7	"	"	1	child.
15	"	"	0	children.

An average of 3.5 children for each parous woman, with 30 per cent nulliparæ. And 66$\frac{2}{3}$ per cent had not had over two children. Only four had been delivered instrumentally.

On the other hand, an analysis of the cases which did not have movable kidney showed that

1	had	had	11	children.
1	"	"	10	"
2	"	"	9	"
1	"	"	7	"
2	"	"	6	"
2	"	"	5	"
6	"	"	4	"
4	"	"	3	"
2	"	"	2	"
19	"	"	1	child.
19	"	"	0	children.

Thus an average for the parous women of 3.2 children, while the nulliparæ composed 32.2 per cent. But there were fifteen cases that had been delivered instrumentally.

Our statistics also show that movable kidney in a colored woman is uncommon, yet an analysis of their pregnancies show the following:

4	had	had	7	children.
1	"	"	6	"
2	"	"	5	"
2	"	"	4	"
2	"	"	3	"
6	"	"	2	"
13	"	"	1	child.
20	"	"	0	children.

An average of 2.8 children for each parous woman, with 20 per cent nulliparæ.

To recapitulate, the nulliparæ composed 30 per cent of the cases of movable kidney, 32 per cent of the cases without movable kidney, and only 20 per cent of the colored women, in whom movable kidney is uncommon.

I believe in many instances, pregnancy and parturition play an accessory part in the causation of movable kidney,

but it is not, as so generally assumed, of such great etiological significance.

Ascites, abdominal tumors, and other pathological conditions causing increased intra-abdominal pressure, may possibly in isolated cases, cause a dislocation of the kidney. But when we consider that nephroptosis occurs in over 20 per cent of adult white women, and that these pathological conditions do not affect 1 per cent of women, it is evident at a glance that they are of no very great significance.

Chronic Constipation.—Some observers, notably Longyear of Detroit, have emphasized constipation as an etiological factor of nephroptosis, especially of the right side. Longyear (American Journal of Obstetrics, Vol. LIV, No. 5) describes bands which he calls the nephrocolic ligaments extending between the large bowel and kidneys, by means of which the latter are dragged down. He says as follows:

> The nephrocolic ligament is formed by an aggregation of fine fasciculi, originating in and being identical with the fibrous tissue forming the framework of the fatty capsule of the kidney, which, after enveloping the kidney in a fine network, passes downward and is inserted into the posterior wall of the ascending colon on the right side, and the descending colon on the left side. Its structure, as well as its action, may be compared to that of a network covering a balloon, the cords of which extend downward and support the car. The kidney is the balloon and the cecum the car. The kidney descends or not, according to the laxity of its supports and the degree of traction exerted on it by the cecum. The cecum consisting of a sac with its outlet upward, the contents of the viscus must be always forced in that direction, which necessitates the application of tractile force in the opposite direction, and as the nephrocolic ligament is a firm and unyielding attachment, the kidney is pulled downward.

He also states that floating kidney is fifteen times more frequent on the right side than on the left.

This theory sounds attractive, but we find the following objections. In the first place, the difference in frequency between the right and left sides is not so great. We found the right kidney prolapsed forty-five times and the left twenty-three times, or a proportion of two to one. In seventeen cases both kidneys were prolapsed in the same patient. Also, in the first hundred and sixty-five nephrorrhaphies in the gynecological service of this hospital, one hundred and twenty-seven were on the right side and thirty-eight on the left, or a proportion of three and a third to one. In ten cases both kidneys were suspended in the same patient. So that Longyear's estimate of fifteen floating right kidneys to one left kidney would seem, both from our dispensary and operative statistics, to be out of all proportion, and that three to one would be more nearly correct. In the second place, a history of constipation was obtained in 49 per cent of white women and in 70 per cent of colored women; or, in other words, white women in whom movable kidney is common do not suffer from constipation as frequently as do colored women in whom movable kidney is uncommon.

Longyear uses this nephrocolic ligament to suspend the kidney, and he has stated his successes and failures so candidly that his work deserves attention; but if this nephrocolic ligament plays an important etiological part in nephroptosis, it must be an anatomical structure peculiarly developed in white women and not in men or colored women, and that is not probable.

Corsets, abdominal bands, and other articles of clothing have been held responsible for nephroptosis. It is very difficult to obtain accurate statistics upon this point, for what one woman considers tight lacing, another would consider only moderate. Becher and Lenhoff examined South Sea Islanders, with whom clothing is an unknown luxury, and found movable kidney just about as often as in civilized races, showing conclusively how small a part clothing plays.

Wolkoff and Deletzine from post-mortem examinations ascribed the preponderance of movable kidney in women to the shape of the renal fossæ. They claimed that in men the niches in which the kidneys lie are rather deep and wider above than below, that is, funnel-shaped; while in women they tend to be cylindrical and wider below, especially on the right side. This seems to be of considerable importance in some cases, for during the operation for suspension of the kidney, it is frequently noticed that the renal fossa is very shallow and occasionally almost absent. As movable kidney is uncommon in colored women, further study upon the shape of their renal fossæ would be interesting and instructive.

As the kidney is held in position chiefly by its capsules, it is possible that a rapid absorption of the fat about the kidney would tend to cause a prolapse. In our series we have been able to obtain a history of acute illness with loss of weight in only a small percentage of cases.

In a recent work, entitled "Movable Kidney a Cause of Insanity, Headache," etc., Suckling has devoted over half of the chapter on etiology to an enumeration of individual cases of nephroptosis following severe injury. I grant that occasionally a blow or fall may cause a descensus of the kidney, but I believe nearly all the cases so classed are due to some other factor, the injury simply attracting attention to a preexisting nephroptosis. Constantly heavy lifting or repeated injury do aggravate a beginning nephroptosis, if there be present the peculiar shape of chest, of which I shall speak later.

If any of the cases of nephroptosis were attributable to gynecological trouble we should certainly expect to find them in a gynecological dispensary. As a matter of fact, in fifty cases, malposition of the uterus was present in thirteen, relaxed vaginal outlet in six, and a small myoma in one; making at the most only twenty cases in which there could be any possible connection between the renal and pelvic conditions and the majority of these seemed to be mere coincidences; while the other thirty had either a normal pelvis or something mild, as a urethritis or salpingitis.

This brings us to the study of the relation between the shape of the chest and abdomen and movable kidney. It is apparent to the casual observer that the chests of women vary greatly. Now the type of chest associated with movable kidney is rather long, narrow, and contracted below, or fun-

nel-shaped. To simply state that a chest is broad or contracted or that an abdominal circumference is large or small, would be very vague indeed. So that I have followed somewhat the example of Becker and Lenhoff and have taken various measurements, three of which I consider cardinal. The first measurement is a vertical one from the suprasternal notch to the top of the symphysis pubis. The second measurement is a circular one at the level of the seventh costal cartilage, that is, in a plane just above the upper poles of the kidneys. The third is the circumference of the abdomen at the level of the umbilicus, which is just below the lower poles of the kidneys. Now what we desire is some means to compare the various forms of chests and abdomens. If we divide this upper circular measurement at the level of the seventh costal cartilage into the vertical measurement from the suprasternal notch to the symphysis pubis, we will obtain a quotient which will serve as an index of the amount of contraction of the chest at that level, that is, just above the upper poles of the kidneys. This we will call Index No. I. If now we divide the lower circular measurement at the level of the umbilicus into the vertical measurement, the result will be an index of the amount of contraction just below the lower poles of the kidneys. This we will call Index No. II. If we divide the lower circular into the upper circular measurement, we will obtain an index of the amount of contraction which takes place between the seventh costal cartilage and the umbilicus, or the portion of the body in which the kidneys lie. This we will call Index No. III.

We will consider first Index No. I. For example, suppose the distance from the suprasternal notch to the symphysis pubis is 48 cm. and the upper circumference is 64 cm., then dividing 64 into 48, and to avoid fractions, multiplying by 100, the result will be 75, which is Index No. I of that particular body. Now from the examination of a large number of white women, the average index is found to be 72.5. Obviously, if the lower part of the chest is contracted, that being the denominator, the index will be high, and for the same reason a broad chest will give a low index.

Now the average index of the woman without movable kidneys is 71.6. There, you see, in women without movable kidney, the index is distinctly lower. In the cases of nephroptosis, there is a relative contraction of the lower part of the chest, and we should expect the index to be high. The average of fifty cases of movable kidney was 77.9.

It has been mentioned before that movable kidney is rare in men. Now in men the chests are broad at their lower portions and the average index is 67.5. Thus, we have an ascending scale: men 67.5, women without movable kidneys 71.6, the normal 72.5, and women with movable kidneys 77.9.

In the series, there were, of course, exceptions, but there was usually some definite reason to account for each exception. For example, one woman, age fifty-five, had bilateral floating kidneys with a low index; but she also had a large emphysematous chest. Previously she may or may not have had the typical chest of floating kidney, but the development of the emphysema distorted the body measurements, so that in her case the index is of no value.

All that has been said applies to Index No. I, or the relative amount of contraction at the level of the upper poles of the kidneys. Index No. II, which we shall next consider, represents the relative contraction just below the lower poles of the kidneys. As you see, we again obtain the same results as in Index No. I, the broad chests of men with the low index as contrasted with the movable kidney chest with its high index. Although here the difference between men and women with non-movable kidneys is not so great.

Examinations of colored women show that Indices Nos. I and II run higher than in white women, and for that reason we would expect to find movable kidney at least as frequent as in white women, but on the contrary we find them much less frequently.

At first sight this would seem to invalidate all our work, but the explanation is found in Index No. III. This, as I have said before, is obtained by dividing the circumference at the umbilicus into the circumference at the seventh costal cartilage. It represents the difference in contraction between those two levels, the upper and lower poles of the kidneys. In the average white woman the upper and lower circumferences are about the same, or in other words, the area of body-cavity in which the kidneys lie is more or less cylindrical. In women with nephroptosis, the lower part of the chest is contracted, consequently the measurement at the seventh costal cartilage is less than at the umbilicus, and is represented by an index of 97.6. In men the lower part of the chest is broad, and consequently the circumference is higher than at the umbilicus, and represented by an index of 106.1.

Right here lies the explanation for colored women. Their circumference at the lower part of the chest is a little larger than at the umbilicus, and is represented by an index of 102.1. They approach the type found in men, but the index is smaller. And, as has been previously shown, movable kidney occurs less frequently in colored than in white women, but not so infrequently as in men.

We could select from our series any number of cases to corroborate this brief summary which I have given, but I have purposely refrained from doing so, for it would be very tiresome and require far more time than is allotted to me.

In conclusion, I would say that pregnancies, chronic constipation, severe injuries, and gynecological conditions, may in a very small percentage of cases, of themselves, cause nephroptosis, and that the peculiar body-shape is not a *sine quâ non.* But in the great majority of cases they are simply accessory, and the true underlying cause, more important than all other factors combined, is the typical body-shape. This may be quickly determined by the three cardinal measurements. In doubtful cases it may be of slight value in diagnosis, but it is especially useful for prognosis when selecting cases for nephrorrhaphy.*

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* Elaborate statistical tables of the cases studied are omitted from lack of space.—Editor.

DISCUSSION OF NEPHROTOMY BY THE SILVER-WIRE METHOD, WITH A REPORT OF TWO CASES.

By Edward H. Richardson, M. D.,

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Kidney surgery is always attended with a certain degree of anxiety because of the danger of hemorrhage. Even the simpler operations upon the kidney, such as fixation or decapsulation, are not exceptions to this rule. Because these operations are usually done through small incisions with imperfect exposure of the vessels at the hilum, and the manipulations necessary for stripping off the fatty capsule or the *Capsula propria*, on the one hand, or for placing the fixation sutures, on the other, may result in rupture of an aberrant vessel, or in lacerations of the cortex that will give rise to very troublesome oozing, or indeed, even to disastrous hemorrhage. The dangers are greatly increased, of course, in operations upon extensively diseased kidneys, in which it becomes necessary to release dense perirenal adhesions, and to deliver the organ outside the body.

Various operations have been devised to lessen the dangers incident to kidney surgery, and to meet specific indications. The prime object of them all, however, is to forestall possible catastrophe through early exposure of the trunk vessels, without too much mutilation. So that in the event of sudden unexpected hemorrhage, the operator will be master of the situation.

Thus one may approach the kidney by the transperitoneal, or the lumbar route. The line of incision may be parallel, perpendicular, or oblique to the longitudinal axis of the body; or it may be a combination of any two of these. Further, it may be a simple muscle-splitting operation without division of muscle fibers, as exemplified by the ordinary kidney fixation through the superior lumbar triangle; or it may be a complete transverse division of the lumbar and hypochondriac parietes, with resection of one or more ribs, and eversion of a large flap of chest wall, in order to expose an enormous hypernephroma, for example. Between these two extremes there are, of course, many possibilities.

There has been developed, therefore, an operative technique in renal surgery that will satisfactorily expose any condition of the kidney that is amenable to surgical treatment. But, curiously enough, this operative technique has been developed almost entirely with reference to the extrinsic renal vessels, and comparatively little attention seems to have been paid to the intrinsic vessels from a surgical standpoint.

Exploration of the kidney, or nephrotomy, is one of the commonest of all operations upon this organ. Hemorrhage is, of course, the chief source of danger; and surgeons employ various devices for its control. One of the commonest is to expose the hilum, and completely shut off the renal circulation temporarily by compression of the renal vessels. Then, at the end of the operation, by transfixing the kidney with mattress sutures of catgut, or by gauze packs, or by a combination of both, the bleeding is controlled.

Another device, used especially in the removal of stones from the kidney pelvis, is to employ specially constructed blunt instruments, or simply an ordinary artery clamp, which, when forced through the kidney tissue, will push aside the larger vessels without wounding them, and permit one to grasp the stone and withdraw it without provoking serious bleeding.

It is obvious, though, that however ingenious such devices may be, an intimate knowledge of the distribution of the intrinsic kidney vessels is of paramount importance in any method of nephrotomy. For if there are certain renal zones relatively free from vessels of any size, through which the kidney can be satisfactorily explored, familiarity with their location is certainly a valuable asset to the operator. It lessens the dangers of the operation, rids the surgeon of much annoyance, and reduces a more complex operation to the category of the simple, in that primary exposure of the vessels at the hilum is rendered unnecessary, and the simple muscle-splitting incisions may be safely employed, rather than the extensive muscle-division ones.

In 1901 Mr. Max Brödel (Johns Hopkins Hosp. Bull., Vol. XII, Jan., 1901) published the results of his elaborate and pains-taking injection experiments on a large series of human kidneys, undertaken to determine the actual form of the kidney pelvis, together with the course and distribution of the larger renal vessels.

From a surgical standpoint this was a most important contribution. It emphasized three points of very great practical value.

First, that at the hilum the renal artery divides as a rule into four or five branches so distributed with regard to the pelvis that three-fourths of the blood supply passes anteriorly, and one-fourth posteriorly. That, the arteries are end-arteries in the strictest sense, the branches of the anterior division never crossing over to the posterior side, or *vice versa*. They do not anastomose with each other.

Second, that while the veins of the two divisions anastomose with each other through two systems of arches, one of which surrounds the bases of the pyramids, while the other encircles the necks of the calyces, yet, through the latter channels, the blood is poured into the larger collecting veins at the hilum, all of which also pass anterior to the pelvis.

Finally, that there are certain surface markings of the kidney that will usually enable the surgeon to determine fairly accurately the location of the planes of arterial division.

The value of these facts in renal surgery is, of course, obvious. Viewed in the light of them nephrotomy becomes a comparatively simple and safe operation, leaving, at first sight, little to be desired as regards operative technique.

E. K. Cullen and Derge (Johns Hopkins Hosp. Bull.,

Vol. XX, Nov., 1909) have just published, however, another most important contribution to the operative technique of nephrotomy.

Basing their work upon the anatomical facts established by Brödel, they undertook two series of experiments on dogs to determine first, whether the direction of the incision in nephrotomy had any appreciable effect on the resulting hemorrhage; and second, whether the bleeding would be less if a silver wire of low tensile strength (No. III) was used instead of the knife in splitting the kidney from within outwards.

They concluded from the first series of experiments, as one would naturally expect from the tree-like branching of the arterial trunks, that the hemorrhage was definitely less when the knife was passed from pelvis to cortex than from cortex to pelvis.

The results of the second series of experiments were even more striking.

By threading the silver wire on a straight liver needle (Konsnietzoff-Cullen), it could be passed through the kidney from pole to pole, or transversely at any level desired, without wounding any vessels of moment, inasmuch as the blunt, flat needle easily pushed aside the vascular trunks lying in its course. With an assistant firmly holding the kidney to prevent undue traction on the vessels at the hilum, the organ was easily divided to any extent desired by a gentle see-saw motion of the wire, with the traction exerted in a cortical direction.

The advantages of the silver wire over the knife were most satisfactorily shown. There was always free bleeding from the cut surfaces where the knife was used, with usually some actively spurting arteries, while following the silver wire divisions, to quote the authors: "How insignificant the hemorrhage may be was well illustrated in one experiment where, after the kidney had been split from pole to pole and the pelvis opened, it was left undisturbed outside the body of the animal while the other kidney was being operated upon. Though the renal vessels at the hilum were not compressed in the least, and the kidney, pulsating synchronously with every heart-beat, was laid open like an open book, there was practically no bleeding from the cut surfaces several minutes after the incision had been made."

It is evident, as the writers go on to state, that very little suturing is necessary after nephrotomy thus performed.

Certainly this work represents a most important advance in renal surgery. It will admit of a wide field of application. It will greatly simplify many kidney operations, and it will in many cases obviate the necessity of a preliminary control of the vessels at the hilum, and thus do away with the necessity of extensive incisions with division of the muscles.

Since the silver-wire method was devised there have been only two cases in the gynecological department in which nephrotomy was indicated.

I was fortunate enough to have the opportunity of operating upon both of these cases on the same day. The silver-wire method was used in both of them, and the results obtained demonstrate conclusively two points. First, the value of the silver-wire method of nephrotomy in certain cases; and second, that the method very clearly has a limited field of application, and should not be employed in every case in which nephrotomy is indicated.

A synopsis of the cases is as follows:

CASE I.—Mrs. M. L. (Gyn. No. 15,672), age 41 years, was admitted to Johns Hopkins Hospital April 6, 1909, complaining of periodic attacks of pain in the right lumbar region.

History.—Twelve years prior to admission she had undergone an abdominal operation in Germany for extensive pelvic inflammatory disease; bilateral salpingo-oöphorectomy being done. Eight years prior to admission she was operated upon in this hospital for renal tuberculosis; a left nephro-ureterectomy being done. For three years following this operation she was treated at intervals in the out-patient department for tuberculous cystitis, which finally cleared up, the patient remaining free from symptoms for three years. The present illness began two years prior to admission with periodic sharp attacks of pain in the right kidney region, which gradually became more severe. About December, 1908, these attacks of renal colic began to recur at intervals of three to four days, with such agonizing pain that the patient was practically incapacitated. The pain was knife-like in character, and radiated along the course of the right ureter to the bladder. She had no chills or sweats with them. Nor had she observed any abnormality in the urine following any attack.

Her general condition at the time of admission last April was good, nothing of importance being discovered on careful physical examination, except slight tenderness on bimanual palpation of the right kidney; which, however, was not perceptibly enlarged, nor was it displaced. There was also considerable thickening felt on vaginal examination about the lower portion of the right ureter. The urine was acid and slightly cloudy, but repeated careful searches for tubercle bacilli gave negative results.

Under general hygienic measures, together with bladder irrigations and instillations the cystitis improved markedly during the first two and one-half months of her stay in the hospital. The attacks of renal colic continued, however, at intervals, so that after the bladder infection had greatly improved, the right ureter was catheterized with a wax-tip catheter. But no evidence of stone was found; and the capacity of the kidney pelvis was normal. The X-ray was also negative. There was, however, always an evening rise of temperature to 99.5° F. About the middle of June the attacks of renal colic became much more intense, and were associated with agonizing bladder spasms, and marked increased frequency of urination. She also had chills, with elevation of temperature to 102° F., and sweats. This condition became so distressing that on June 28 I made a vesico-vaginal fistula, in order to put the bladder at rest, and instituted continuous bladder irrigations for five hours daily.

Following this operation the attacks of renal and bladder pain entirely disappeared. The patient's general condition greatly improved, and the bladder cleared up entirely by August 10. So that on this date I operated again and closed the fistula, which healed perfectly throughout.

Eight days after this operation, however, the old pains returned again with increased severity, and the patient rapidly became seriously ill. She had constant fever of 102°-103° F., with daily chills, profuse sweats, nausea and vomiting. She took very little nourishment, and lost weight rapidly; her condition by the first week in September becoming critical.

She suffered so intensely that she begged to have the kidney explored, even after understanding fully the dangers of neph-

rotomy in her poor general condition, and with only one kidney, which was probably diseased; saying that she greatly preferred to die under the operation than to longer endure the pain.

On September 8 I exposed the kidney through the superior lumbar triangle, and after considerable difficulty, owing both to the fact that it was hypertrophied to nearly double normal size, and was also quite densely adherent about the upper pole, I succeeded in delivering it intact outside the body. Nothing abnormal could be felt either in the kidney itself, the pelvis, or the upper portion of the ureter.

I then passed a long, straight liver needle, carrying a number III silver wire. into the kidney at the lower pole close to the hilum, and out a little posterior to the mid-point of the convex border. The capsule between the two ends of the wire was then incised along the convex border, and by exerting gentle traction, with a see-saw motion of the wire, the lower half of the kidney was laid open. The needle was then re-entered in the depths of the wound and caused to emerge at a point on the upper pole corresponding to the one at which it had been introduced on the lower pole. The upper half of the kidney was then similarly divided, and the entire organ opened like a book, with the pelvis clearly exposed to view. The large size of the kidney forced us to do the bisection in two stages, because the longest available needle was too short to reach from pole to pole.

The trifling amount of bleeding from the cut surfaces of the kidney was indeed remarkable, although no compression whatever was being exerted on the vessels at the hilum. After carefully examining all parts of the kidney and its pelvis, the two halves were again brought together, and a few mattress sutures of catgut served to completely check the slight venous oozing.

Unfortunately, we found nothing whatever to account for the renal crises. There were a few scattered pin-head sized areas that looked suspiciously like tuberculosis, but no definite tubercles were seen.

Curiously enough, however, the patient was very greatly benefited by the operation. Beginning a few days afterwards she began to improve. She has had only one slight attack of pain in the past two months, has gained eight pounds in weight, and is now up and about the ward daily.

Case II.—Mrs. B. J. (Gyn. No. 16,006), age 31 years, was admitted to Johns Hopkins Hospital on September 2, 1909, complaining of chills and pain in the right side.

History.—The family and past histories are unimportant. The present illness began eight months prior to admission with pain on urination and increased frequency. No blood but much pus had been noticed in the urine. During the past month prior to admission she suffered with periodic attacks of sharp pain in the lower right abdomen. The pain did not radiate. She had chills, elevation of temperature to 104.5° F., sweats, nausea, and vomiting with the attacks, which recurred with striking regularity every day. The duration of an attack was from 1½ to 2 hours. She had lost 20 to 30 pounds in weight.

The general examination on admission showed that the patient was quite ill. She looked anemic, and had evidently lost much flesh. There were suspicious signs of an early pulmonary lesion at the left apex. The right kidney was not enlarged, but was tender on palpation. The blood examination was negative for malaria, but showed a leucocytosis of 12,000. The cystoscopic examination showed a normal bladder; clear, normal urine from the left kidney; turbid, purulent urine from the right kidney. No tubercle bacilli were found in the urine. The wax-tip catheter and X-ray were both negative, no evidence of stone in the right kidney and ureter being found.

Operation.—On September 8 I exposed the right kidney through the superior lumbar triangle, and easily delivered it outside the body without division of any muscle fibers. I could not detect any abnormality from inspection and palpation either of the kidney itself, or of the pelvis and upper portion of the ureter. I then transfixed the kidney from pole to pole with a straight liver needle, carrying a silver wire. The kidney was then opened as already described. But in this case at several stages of the bisection very considerable resistance to the passage of the silver wire was encountered, so that quite strong traction was necessary to completely divide the organ. When it was laid open the cause for this was evident. The kidney contained several small abscesses. The largest one was situated in the upper pole and measured about 2 cm. in diameter. These abscesses were surrounded by dense fibrous tissue walls, which were more resistent than the kidney parenchyma and the vessels. Consequently, strong traction on the wire was necessary to divide them, and as a result of this many more vessels were torn open than would have been the case had a knife been used, and a clean cut made from within outwards. The bleeding was also very profuse, and it became necessary to compress the vessels at the hilum to control it. A nephrectomy being indicated, the renal vessels together with the ureter were skeletonized, clamped and divided, and the kidney removed.

The patient stood the operation well, but on the second day of her convalescence, her temperature reached 104° F., and she complained of pain in the right side of her chest. Upon examination we found a small patch of pneumonia, with a friction rub easily heard over it.

Fortunately, this rapidly cleared up, and her temperature reached normal on the ninth day after operation. She then improved rapidly, and was discharged well on October 12, 1909.

From these two cases we can draw several important practical lessons. The first case is a type of by far the larger group of kidney cases in which nephrotomy is indicated; and it corroborates fully the claims made by Cullen and Derge as to the advantages of the silver-wire method.

The second case, on the other hand, clearly represents a group of cases in which the silver-wire method of nephrotomy is distinctly contraindicated for two reasons. First, whenever abscesses, fibrous tissue, or other pathological conditions in the kidney render it necessary to exert strong traction on the wire in order to bisect the organ, many vessels will be lacerated, and consequently both the damage to the kidney parenchyma and the hemorrhage will be greater than if a knife were employed. Second, the pulmonary complications in the second case following operation show conclusively the dangers of omitting compression of the vessels at the hilum, and thus permitting free renal circulation while doing a nephrotomy on an infected kidney. I feel sure that in this case an infected embolus was swept into the renal vein, thence to the vena cava, right heart, and finally lodged in the right lung, where it produced a localized pneumonia.

It must be remembered that the work of Cullen and Derge was all done on normal kidneys, and that the mechanics of the method precludes its rational application to a group of cases illustrated by our second one. In the vast majority of cases, however, by combining the silver-wire method of nephrotomy with the anatomic points established by Brödel, one obtains a most satisfactory operative technique.

In conclusion, it should be emphasized that complete longi-

tudinal bisection of the kidney is comparatively rarely indicated. The non-vascular zones are so clearly marked that one can make transverse divisions of the parenchyma and open the pelvis at almost any level desired; or one can safely combine a transverse with a longitudinal division, if it be indicated. I am inclined to think, too, that the silver wire method has a further very important field of application, and that is in partial nephrectomy, an operation now less commonly done than, I believe, will be the case within another decade.

ANTI-TYPHOID VACCINATION. THE IMMEDIATE RESULTS OF THE ADMINISTRATION OF 3600 DOSES.*

By MAJOR F. F. RUSSELL,
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The history of anti-typhoid vaccination is short and quite well-known, and it will hardly be necessary to do more than mention a few facts. In India Haffkine had obtained a considerable measure of success in the prevention of cholera by means of prophylactic inoculations, and this, in connection with the experimental work of Pfeiffer, led Sir Almroth E. Wright to take up the subject of vaccination against typhoid. Pfeiffer had informed Wright, in the course of a conversation, that it was not necessary to inoculate living cultures into animals to produce agglutinins, but that these anti-bodies could also be produced by the injection of killed typhoid bacilli. The idea apparently presented itself as feasible to both Pfeiffer and Wright that other anti-bodies, sufficient in quantity to protect against typhoid fever, would also be formed in response to the inoculation of killed typhoid bacilli into human beings, for Wright reported his first two cases of immunization in human beings in 1896,[1] and Pfeiffer and Kolle reported the result of anti-typhoid vaccination in two men later in the same year.[2] Although this paper covers only two cases it is very convincing because of the completeness of the investigation, for not only was an increase in the agglutinins found to follow a single dose of vaccin, but also a very considerable increase in the bacteriolytic power of the blood when tested according to Pfeiffer's well-known method with guinea-pigs. At this time Pfeiffer suggested the use of vaccin to limit the spread of epidemics, and its use in time of war. In January, 1897, Wright[3] made a further and more complete contribution to the subject in which he reported the results of the use of anti-typhoid vaccin in 18 people.

Although Wright was more or less indebted to both Haffkine and Pfeiffer for helpful suggestions, there is no doubt but that to him belongs the principal credit for placing prophylactic vaccination against typhoid on a practical working basis.

In 1898 he vaccinated about 4000 men of the British Indian Army,[4] and in the years from 1899 to 1902 he furnished 400,000 doses to the English troops in the Boer War. It is reported that 100,000 inoculations were made, but not very much has as yet been published about the results in South Africa, and it is improbable that we shall get any further statistics of value from that campaign. The only figures which I have been able to find[5] show that 19,000 men were immunized and that the incidence of typhoid among them was only about half as much as among the untreated, and that the death rate was diminished about two-thirds.

In the latter part of 1902 considerable opposition to the inoculations developed in the English service, and they were discontinued. A Commission[6] was appointed to investigate the whole subject, and as a result the practice was reintroduced into the service in October, 1904. In the meantime Sir A. E. Wright had severed his connection with the English Army, and the work was carried on by Colonel Leishman and his assistant, Major Harrison, of the R. A. M. C.

Many thousands of doses have been given since then, and Leishman[7] has given the results of the immunization of 5473 cases. These men all belonged to 16 regiments which had been selected for a carefully-controlled investigation on a large scale. As each of these regiments was in turn ordered to service in India, a medical officer, who had been especially trained for this particular duty, was attached. He lectured to the troops on the prevention of the disease, and called for volunteers and immunized them.

As this medical officer is always present with the regiment in all its journeys, he is able to keep careful records of all men immunized, and to care for, and to vaccinate additional volunteers and recruits from time to time as opportunity offers. From his knowledge of typhoid fever and clinical laboratory methods he is enabled to make an accurate diagnosis in all suspicious cases. By means of these precautions Colonel Leishman is able to furnish statistics which are thoroughly accurate and reliable.

TABLE.

Inoculated, 5473. Cases of typhoid fever, 21. Deaths, 2, or per 1000 inoculated cases, .36.

Non-inoculated, 6610. Cases of typhoid fever, 187. Deaths, 26, or per 1000 non-inoculated cases, 3.93.

Among 12,083 men there were 5473 inoculated, and 6610 uninoculated. Among the former there were 21 cases of typhoid with two deaths, and among the latter 187 cases and 26 deaths. Among the exposed regiments who had been inoculated with the vaccin in use at present there were 3.7 cases per 1000 against 32.8 per 1000 among the untreated. Only four out of the 21 vaccinated men who subsequently developed

* Read before the Johns Hopkins Hospital Medical Society, December 6, 1909.

typhoid had had two doses of the vaccin, and they all recovered. The other 17 had received only one dose. The observations of this group of 12,000 men covers a period of over three years, and no more perfect or convincing statistics are needed to show the value of this method of prophylaxis.

There are very few facts as yet on which we can base a statement as to the duration of the protection. The English statistics just quoted show that it will last for at least three years, and from the army point of view, if it lasts three years that is long enough, for no modern war will last as long as that. Three years will also cover the period of service of hospital internes and the training period of nurses, and by vaccinating them you can reduce the number of cases to half or even less, and such a result would justify you in insisting upon its use among people whose vocation exposes them to infection. It is of course quite illogical to conclude that the immunity ceases with the disappearance of the specific anti-bodies from the blood, since agglutinins, opsonins and bacteriolysins all disappear after typhoid fever in the course of a few months, as a rule, and yet the immunity lasts for many years if not for life. We may compare the evolutions of the body cells after vaccination to the evolutions of troops undergoing training during maneuvers and the real attack of typhoid fever to the battle of actual war. If the cells have been trained in organized defense and offense during the artificial immunization with harmless vaccins, they are better able to mobilize promptly and properly and to suppress the invading organisms during the incubation period. If they are not successful in completely preventing the outbreak they are at least more apt to be victorious than untrained cells which are having their first struggle with the typhoid enemy.

The results of anti-typhoid vaccination in the German Colonial Army in the Herero campaign in 1904 in Southwest Africa were also quite favorable.[8] Eight thousand men were vaccinated according to the method of Pfeiffer and Kolle, and the difference in the incidence and death rates are shown by the following table:

		Cases.	Deaths
Per thousand of strength.	Unvaccinated	98.4	12.6
" " "	Vaccinated	50.9	3.3

Roughly, there were about half as many cases and only a quarter as many deaths among the vaccinated.

The *necessity* in the army for some such procedure as vaccination, and the inadequacy of other means of prevention is shown by the very great prevalence of this disease in modern wars. In the Civil War we had 80,000 cases in the Northern Army. In the Franco-Prussian War there were 73,396 cases and 8789 deaths among the Germans; in fact 60 per cent of their total mortality was due to typhoid. During the Boer War there were 31,000 cases and 5877 deaths. In the Spanish War we had 20,730 cases and 1580 deaths among 120,000 men or one case in 5.6 men. Eighty-six per cent of all deaths were due to this disease. We have no data as yet with reference to the Manchurian War.

In the event of a war to-day there is every reason to believe that we could obtain much better results in prevention than in these wars, but the number of cases would still be large, very large, in spite of the advance of our knowledge of the epidemiology of this disease during the last ten years.

The Preparation of the Vaccin.

It has been shown by Wassermann and Strong[9] that it is not necessary to use a virulent or freshly isolated culture in making typhoid vaccins. It is necessary, however, to select a culture which has good binding powers and which will produce large quantities of anti-bodies when injected into men and animals. The culture which we use was isolated from the spleen of a fatal case many years ago. It is a typical typhoid in every way and grows luxuriantly and agglutinates well with immune serum. Its virulence has not been tested lately but it is probably quite safe to characterize it as an avirulent culture. It is grown on agar slants for 18 or 20 hours, and is then washed off in a small quantity, about 2 cc., of physiological salt solution. The agar tubes are of uniform size and sloped in a uniform way on racks built for the purpose. They are sowed with a uniform quantity of a broth suspension of a 20-hour agar growth. Every effort is made to obtain two or three hundred agar tubes with the same amount of growth. They are all looked over and any which do not come up to the standard are discarded. It has proven in practice quite a simple matter to obtain a standard 20-hour growth with substantially no variation from month to month. The emulsion is well shaken to break up clumps, and a sample is taken for a bacterial count and for tests of purity of the culture. The emulsion is then filled into large (50 cc.) tubes which are sealed in the flame of a blow-pipe. The sealed tubes are then sunk in a water bath which is furnished with an electrically-driven stirring apparatus to secure an equal temperature throughout. The bath is heated to 60° C., and the tubes are kept submerged for 75 minutes, since experiment has shown that it takes 15 minutes for a large quantity of material to reach the temperature of the bath. The bacteria are therefore killed by heating to 60° C. for one hour. We have never succeeded in killing the cultures with certainty at lower temperatures or shorter exposures than this. After the cultures are thus killed, the concentrated emulsion is diluted up to about 15 to 20 cc. for each agar slant. The quantity varies somewhat as the bacterial count serves as a check, and may indicate that a little more or a little less salt solution to the tube is necessary to give a product containing 1,000,000,000 bacteria to the cubic centimeter. Before the vaccin is put into ampullæ there is added one-quarter of 1 per cent of tricresol as a matter of safety.

The vaccin is administered to two animals at least, a mouse and a guinea-pig, before any is used on human beings. The experience with tetanus in India and plague in Manila, from contaminated vaccins, has shown that this precaution is necessary. Ærobic and anærobic tests for sterility are also made on each batch of vaccin.

The Keeping Qualities of the Vaccin.

Our oldest vaccin has now been kept in the ice-box for 15 months, and inoculations into animals and man show that it is just as effective as when first prepared.

Recent Experience with Vaccin.

The vaccination of officers and enlisted men in our army was begun in February of this year (1909), and up to the present time completed records of the vaccinations of 1400 individuals have been collected.

As the work of the first year was looked upon as merely preliminary we have attempted to collect statistics as to the immediate results in the way of local and general reactions, for it was realized that any measure like this which is purely voluntary, must not be too unpleasant, painful or disagreeable, if it is to be popular.

Each dose of vaccin is followed by a local reaction which varies very little either with the size of the dose or with the idiosyncrasy of the individual. As a rule, there is a red and tender spot about as large as the palm of the hand at the point of inoculation. This begins to appear in six to eight hours, and reaches its full development in about 12 hours, and then gradually subsides and disappears, as a rule, in 48 to 72 hours. It happens occasionally, especially in children, that there is little or no local reaction, but this is rather a rare occurrence. Occasionally the red and swollen area may be unusually large and extend from the point of inoculation to the elbow or even half way to the wrist. The excessively severe local reactions are not particularly painful, and the men are able to use the arms for light work without discomfort; and it has never been necessary to make local applications to the arms, or to put the arm into a sling. The severe local reactions subside about as quickly as the average and there are fortunately not very many of them. The local reaction extends up the arm to the axillary glands in a considerable number of instances. The lymph nodes are slightly swollen and tender on pressure, and occasionally the man will call attention to them. The symptoms referable to the glandular swelling disappears in about 24 hours and are never followed by permanent enlargement or by suppuration.

At the seat of the inoculation a small hard bullet-like nodule may persist without giving rise to any symptoms for a week or two before it subsides. No instance of the continued presence of this nodule beyond a couple of weeks has come to my knowledge, and the local reaction regardless of its severity passes away completely and leaves no scar or mark of any sort to show where the vaccination has been made.

The general reaction varies in its symptoms much more than the local. In children and in many adults it can be truly said to be absent. In its milder form it causes a transitory headache and a feeling of weariness which lasts from two or three hours to a day. Slightly more marked general reactions are evidenced by considerable headache and a decided feeling of lassitude which lasts until about noon of the following day. Occasionally there are chilly sensations without much rise of temperature. A few men have complained of nausea and a very few of diarrhœa lasting for a day or part of a day. It is rather interesting to note the way in which the men themselves describe a mild reaction. So many have now expressed themselves in the same way that it seems proper to mention it here. They say "I thought I was going to have a sore throat" or "a cold" or "an attack of the grip, but as it passed off quickly I realized that it was the effect of the vaccination."

The moderate reactions are characterized by a rise of temperature to 101° to 103° F. A few have had chills, and have had the symptoms described above in a rather more pronounced form. They constituted only a small percentage of the total.

The severe reactions are those with a temperature of 103° F. and above. Most of these men report having had a chill with more or less headache, nausea, vomiting or herpes labialis; no cases of albuminuria have been reported. We have taken especial pains to obtain full reports of all severe reactions, as it was realized from the beginning that if many occurred it would interfere greatly with carrying through the immunization of the army, and it is consequently gratifying to be able to report that very few of the vaccinations have been followed by severe reactions. We do not yet know what the conditions are which bring about the moderate and severe general reactions.

The fact that a man may already have had typhoid fever at some time in the past seems to increase the chances of a moderate or severe reaction. Up to the present (December, 1909) we have collected records of the vaccinations of 124 such cases and reference to the chart on this page will show an undoubted difference in the severity of the reactions of those who have had, and those who have not had, typhoid.

The 124 cases who had previously had typhoid were arranged in seven five-year groups in the hope that this would show how long the hypersensitiveness to typhoid lasted, but the figures are inconclusive. Apparently it lasts for 30 to 35 years, but the number of cases is quite small, and other factors, such as advancing age, may be equally important in giving a high percentage of moderate and service reactions.

TABLE.

Cases.	First Dose.				Second Dose.				Third Dose.			
	None.	Mild.	Moderate.	Severe.	None.	Mild.	Moderate.	Severe.	None.	Mild.	Moderate.	Severe.
1204. No typhoid	59.9	31.4	7.5	0.9	67.8	25.6	5.3	1.1	77.2	19.2	3.0	0.4
124. Typhoid	60.4	25.8	12.0	1.6	64.6	23.2	10.3	1.7	75.0	19.5	5.4	0.0
26 within 5 years........	50.0	34.6	15.3	0.0	78.2	17.3	4.3	1.7	71.4	18.9	9.5	0.0
33 " 10 "	57.5	24.2	15.1	3.	45.1	41.9	9.6	3.2	72.7	22.7	4.5	0.0
29 " 15 "	72.4	20.6	6.8	0.	71.4	21.4	7.1	0.	84.	12.	4.	0.
9 " 20 "	55.5	33.3	11.1	0.	65.5	12.5	25.	0.	57.1	42.8	0.	0.
7 " 25 "	57.1	28.5	14.2	0.	50.	50.	0.	0.	75.	25.	0.	0.
4 " 30 "	100.	0.	0.	0.	100.	0.	0.	0.	75.	25.	0.	0.
5 " 35 "	40.	20.	20.	20.	60.	0.	20.	20.	50.	50.	0.	0.

Not every case of typhoid leaves the patient in this hypersusceptible or anaphylactic condition, and the fact that such

people give a higher percentage of severe reactions than individuals who have not been sensitized by an attack of the fever was not appreciated until a considerable number of record cards had been examined. The number of cases tabulated (124) is so large that the increased severity can hardly be a

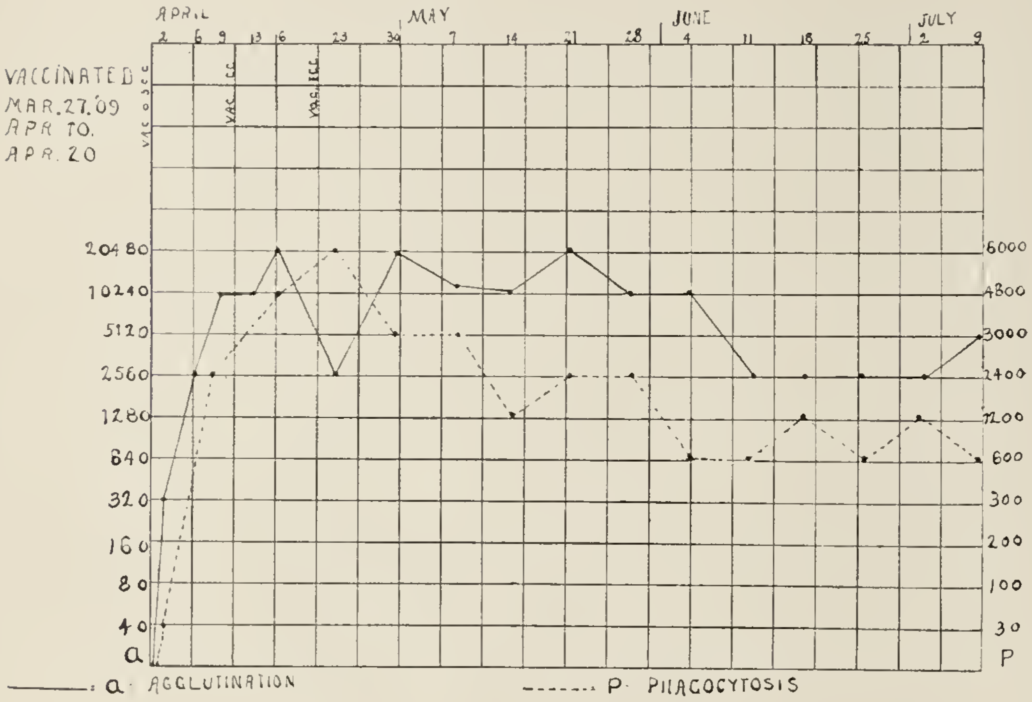


Chart I.

coincidence. Presumably it is coupled with an immunity to typhoid and it therefore is not to be classed with the hypersusceptibility of man or animals infected with tuberculosis and glanders. To what extent it may indicate residual typhoid affections of the bile tract, urinary tract or intestines, is at present unknown. Previous typhoid will not, however, explain all of the marked reactions.

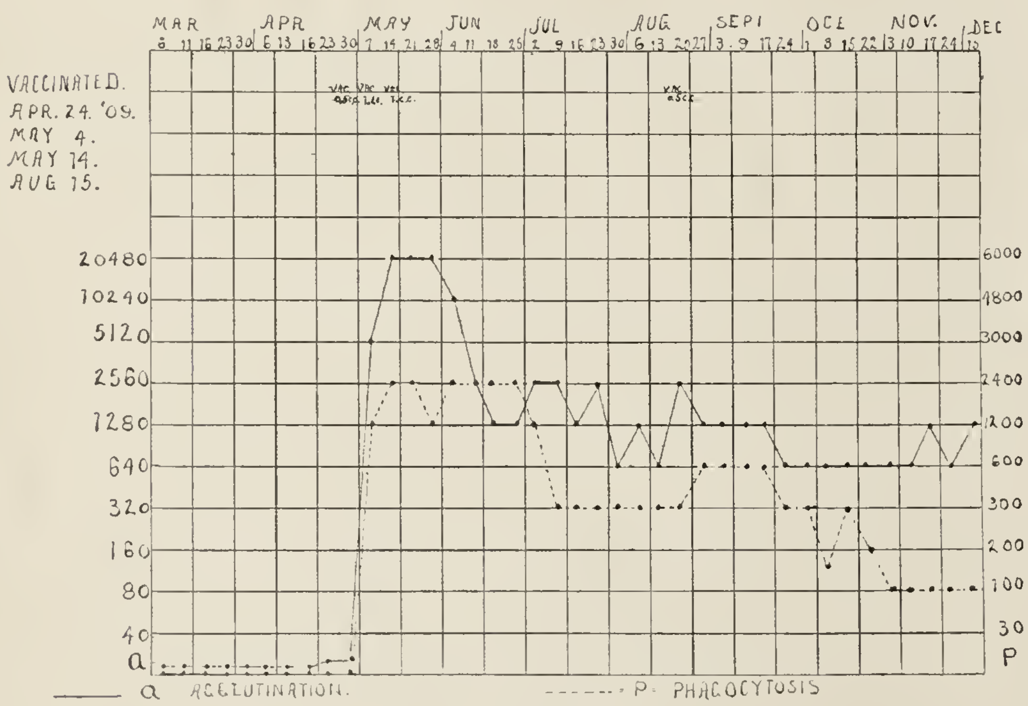


Chart II.

It is well known that the severity of typhoid varies in different epidemics, and also among individuals in a single epidemic, and one of the causes commonly assigned for this individual variation in severity is the varying susceptibility, or better, the varying resistance of the patient, and in default of any better explanation it seems reasonable to believe that the patients who show the greater susceptibility to the vaccin are those who would present the least resistance to the disease if naturally infected with the living typhoid bacillus.

Examination of the blood serum after vaccination has been made of a large number of cases and as the results are, as a rule, quite similar, the exhibition of two charts, I and II, will suffice as an example. They are neither better nor worse than many others, and are offered here merely because they cover a greater period of time and greater number of examinations than any others which we have made. The men were vaccinated in March, 1909, and weekly observations on the agglutination and on phagocytosis have been made regularly. No curve of bactericidal power is shown for we have not yet been able to get any method which will give *in vitro* altogether satisfactory results over a long period.

All agglutinations are done by the macroscopic method, and the serum dilutions are made with great care, and can be considered quite accurate. An increase in the agglutination is often evident on the fourth or fifth day, and by the sixth to eighth day a considerable increase is always noted. The curve shoots up rapidly to 1-10,000 and even to 1-20,000. The fall begins in about six weeks and continues to approach normal more or less slowly so that at the end of 15 months in my oldest case it is not evident in dilutions above 1 in 80 to 1 in 100. In exceptional cases the curve is neither so high nor so long as in the chart exhibited. The curve of phagocytosis is equally well marked. The rise is sharp and high and the titer reached is usually 1-5000. It falls more rapidly than the agglutination curve, but even after 10 months in the oldest case it has not yet dropped to normal. We encountered rather more trouble in developing a satisfactory routine technique for this test than for the agglutinations, and our observations consequently do not go so far back. The opsonic index when obtained by ordinary methods fails completely and the dilution method of Neufelt is therefore used. At first the capillary pipettes of Wright, and human leucocytes, were made use of with progressive dilutions of the serum and salt dilution and normal serum controls. The titer of the serum is expressed by the highest dilution in the final mixture, which showed more phagocytosis than the controls. Thus the primary serum dilution, 1 in 10, 1 in 100, would become when diluted with equal volumes of leucocytes and bacterial emulsion, 1 in 30, 1 in 300, etc. By this method a rapid inspection of the slides eliminates all the dilutions in which the phagocytosis is marked, and only the controls and those slides on the border line remain to be counted. In the last few months we have adopted the Neufelt method *in toto*, since in practice it takes much less time and is quite simple. The leucocytes are obtained from guinea-pigs after aleuronat injections into the peritoneal cavity, and the mixture of leucocytes, serum and bacteria is made in small test tubes. The serum is inactivated at 56° C. for 30 minutes and the mixture is incubated for two hours at 37°, when smears are made and stained with a polychrome methylene blue.

We have found the strain of typhoid bacillus to be very important. All our old cultures, and even many recently isolated ones, are phagocyted spontaneously to such an extent that little

difference can be seen between the controls and the serum to be tested. After searching through all our stock cultures and many recent isolations we selected strains obtained by blood cultures in the early stages of typhoid fever which are almost completely resistant to spontaneous phagocytosis, and these strains have been transferred at infrequent intervals, and only one out of the several selected has since degenerated to the same condition as the older cultures. With a suitable culture of typhoid, guinea-pig leucocytes and a rather long period of incubation, we found no difficulty in getting regular and well-marked determinations of the phagocytic power of the serum.

The leucocyte count is temporarily but regularly increased after each dose of vaccin. The rise is often to 15,000, and the fall is gradual and reaches normal in about a week.

The accompanying chart shows graphically the percentage of severe (103° F. or over), moderate (100° to 103° F.), mild (up to 100° F.) or absent general reactions in various groups. The total reactions recorded is 3640 of which 0.9 per cent were severe, 5.7 per cent moderate, 25.3 per cent mild, and 68 per cent absent. The same number of reactions grouped according to doses shows the following:

	1st Dose.	2d Dose.	3d Dose.
Severe	1.0%	1.2%	0.3%
Moderate	7.7	5.6	3.1
Mild	30.7	24.9	18.7
Absent	60.5	68.2	77.8

The reactions of those who have never had typhoid are as follows (1204 persons):

	1st Dose.	2d Dose.	3d Dose.
Severe	0.9%	1.1%	0.4%
Moderate	7.5	5.3	3.0
Mild	31.4	25.6	19.2
Absent	59.9	67.8	77.2

The reactions among those who had had typhoid is as follows (124 persons):

	1st Dose.	2d Dose.	3d Dose.
Severe	1.6%	1.9%	0.0%
Moderate	12.0	10.3	5.4
Mild	25.8	23.2	19.5
Absent	60.4	64.6	75.0

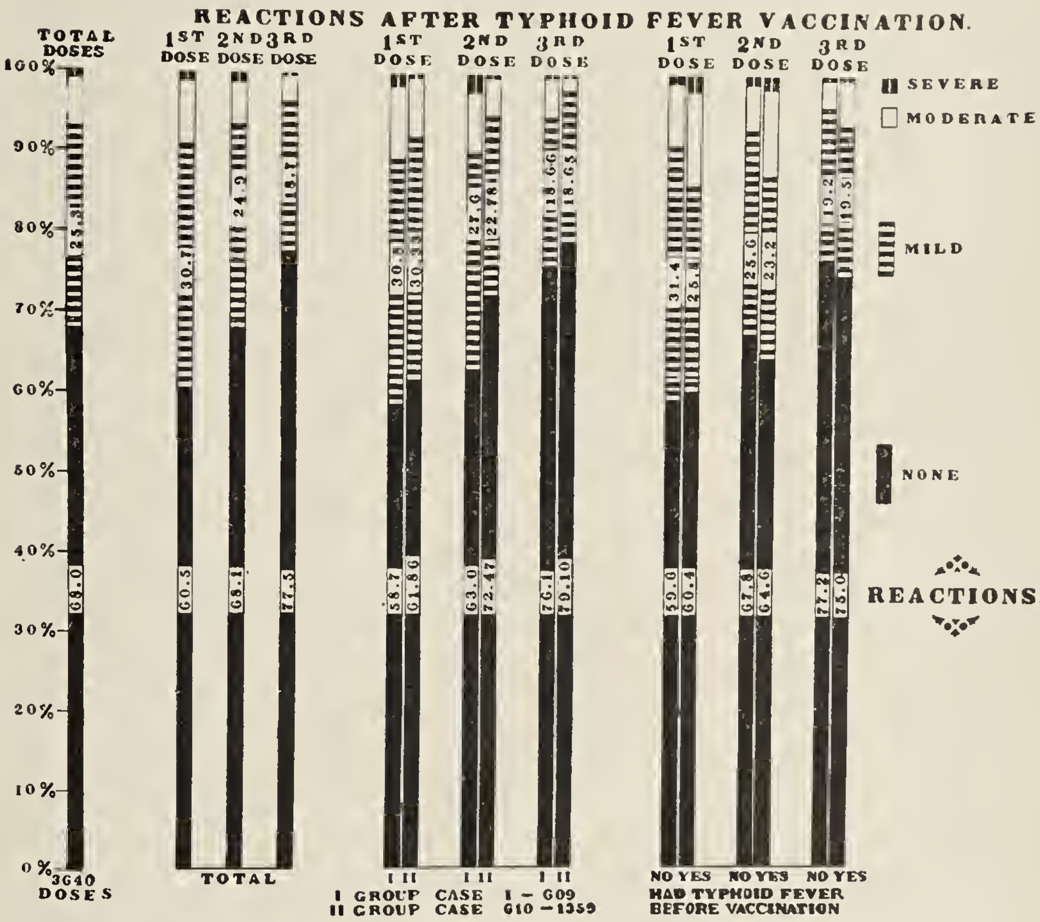
In order to learn whether we were making any progress in eliminating the unpleasant effects of the vaccination, the first 609 cases vaccinated are compared with the last 750. The graphic method shows by a glance at the chart that we have made decided progress in this direction, and that the number of unpleasant reactions has been reduced considerably.

Up to the present time applicants have been vaccinated without regard to age and a few people of 50 or more years of age have been treated, and the reactions have been tabulated in 10-year periods, and it is seen from the accompanying table that the percentage of cases in which the reaction is absent decreases with the increase in age and the percentage of mild reactions increases: there is no very marked difference in the moderate and severe reactions at different ages. On the whole, one may say that the younger the applicant the less marked the general reactions.

The Percentage of Different Reactions at Varying Ages.

Age.	First Dose.				Second Dose.				Third Dose.				
	Absent.	Mild.	Moderate.	Severe.	Absent.	Mild.	Moderate.	Severe.	Absent.	Mild.	Moderate.	Severe.	
0 to 10	73	20	06	00	100	00	00	00	93	07	00	00	15 cases.
10 " 20	80	14	04	01	81	16	01	00	94	03	02	00	97 "
20 " 30	61	31	06	01	71	22	04	01	81	15	03	01	595 "
30 " 40	50	39	09	01	62	26	08	01	73	22	02	01	153 "
40 " 50	42	46	08	01	61	26	07	03	70	29	00	00	24 "
50 " 60	33	60	06	00	46	53	00	00	54	45	00	00	5 "

In children both the local and general reactions are exceedingly mild and cause little or no inconvenience.



The history of the prophylactic use of anti-typhoid vaccin goes back, as we have seen, to 1898, and it is in some ways a matter of surprise that a method which promises so much has been used so little. It can be said that it has scarcely been used outside of the English, German and American armies. The reasons for the failure of the method to become popular in civil life, especially in hospitals, institutions, and among gangs of laborers employed on railroads and public works, are worthy of some study. It will help to place the conditions clearly before us if we consider for a moment the procedure carried out on the appearance of an epidemic of smallpox. In that event all contacts are immediately vaccinated. The newspapers call attention to the presence of the disease and many people seek protection at public vaccinating stations or at the hands of their family physicians. In addition all children must, as a rule, be vaccinated before they can be admitted to school. All recruits for the army and navy

are vaccinated as soon as they are sworn in. These general rules are of course the result of years of experience with smallpox, for at one time vaccination in smallpox was in much the same chaotic condition as vaccination against typhoid to-day. We are met at the very beginning in the case of typhoid with such statements in modern text-books as this:[10]

> The immediate effect of the vaccination is to diminish the resistance to infection by typhoid bacilli, and if large doses have been given this diminished immunity may be very marked. With this there is a great increase in both the bactericidal and agglutinating elements in the blood. With small doses the increased immunity is less and persists for a shorter time. This has led Wright to advise the giving of two weaker injections in preference to one strong one. . . . It is evident that it would not be wise to vaccinate during an epidemic as the procedure apparently makes the individual less resistant to infection for a time.
>
> It is difficult to predict to what an extent vaccination against typhoid fever may be used in the future. It would certainly seem wise to carry it out among troops who are going to infected districts. In epidemics it should not be used, as already noted. The troublesome symptoms which occur immediately after the injection should not be considered as a contra-indication.

If we are to be guided by the opinion of this writer we would not be able to use the method in stamping out an epidemic but must confine ourselves to long-range prophylaxis.

Another reason for the lack of appreciation of the value of this measure has been the idea that it produced violent reactions and gives the patient not only a very sore arm but also a good deal of prostration, and often headache, fever and chills. A report published by Flemings, of the German Army, is largely responsible for this. He found that 97.1 per cent of his cases developed fever and that the average was 38.4° C. The highest was 40.3° and the lowest 37.2° C.

There were chills in 63.1 per cent, headache in 61.2 per cent, and vomiting in 19.4 per cent. Loss of appetite occurred in practically all cases. Albuminuria was present in two out of the 91 treated. Herpes labialis occurred in 19.4 per cent.

The vaccin used by Fleming was prepared according to the method of Pfeiffer and Kolle, and is much stronger than ours. They obtain only 5 cc. of finished vaccin from an average agar slant while we get about four times as much, and this excessive dosage is probably responsible for the severe type of general reaction obtained. It is also true that many of the earlier vaccinations, even those carried out by Sir A. E. Wright, were made with quite large doses and there were, no doubt, a good many severe and prostrating reactions. The dosage in the early days was based largely on the result of inoculations in animals, and was to a certain extent misleading as the usual laboratory animals are not susceptible to the disease, and are relatively resistant to the endotoxins. Now that we have found as a result of many thousand vaccinations in human beings, a more suitable and sufficient dose we are no longer troubled to any considerable extent with the severe reactions.

The greatest of all obstacles with which we have to contend, however, is the very prevalent idea of the negative phase: the idea that an individual is more apt to contract typhoid fever for a short time after vaccination than he would have been had he not been immunized. The expression "negative phase" we owe to Sir A. E. Wright, who stated that there is a drop in the anti-toxic and bactericidal content of the blood for a short period following a dose of the vaccin. He quotes Ehrlich and Madsen to the same effect. Reference to his paper will show, however, that he was not dealing with the effect of the first dose, but with the effect of a dose of toxin on an animal already immunized. Ehrlich's and Madsen's studies were made on the effects of the administration of diphtheria and tetanus toxin and not with typhoid or any of the group of bacteria which act through insoluble or endotoxins. There are good reasons for believing that behavior of these two groups of bacteria is quite different. Because a negative phase and increased susceptibility to the toxin developed after a time in horses used for the production of diphtheria antitoxin, we should not infer that a period of increased susceptibility follows the injection of killed typhoid bacilli or any other of the bacteria which do not produce exotoxins.[11] It does not appear that the effect was to diminish the quantity of protective anti-bodies below the normal, but merely somewhat below the level attained during a preceding immunization. In the same paper he gives several curves of the bactericidal power of the blood following anti-typhoid vaccination. In two of these there is shown a decided drop below the normal after the first vaccination, in a third there is a very small negative phase of bactericidal power, and in the fourth there is a complete suppression of the negative phase. Wright's[12] own conclusions as to the practical importance of the law of negative and positive phase in connection with prophylactic inoculations undertaken with living or sterilized vaccins are as follows:

> In considering, in the light of individual results obtained in certain series of anti-typhoid inoculations undertaken in actually infected surroundings, the significance of the negative phase of bactericidal power after anti-typhoid inoculation, I have called attention to the fact that the success of these prophylactic inoculations is imperiled where excessive doses of vaccin are administered to patients in actually infected surroundings, or immediately before transference to such surroundings. Basing myself upon information collected in India by the Indian Plague Commission, in connection with Mr. Haffkine's anti-plague vaccination, I made a similar suggestion in connection with this prophylactic inoculation. And I have recently learned that the idea of a risk attaching to the inoculation of large doses of vaccin in infected surroundings suggested itself also to several observers in South Africa who had occasion to watch the effect of the anti-typhoid inoculation there undertaken. If the suggestion made by me in connection with anti-typhoid and anti-plague inoculation are justified, we may not reasonably expect to find indications of an increased susceptibility to smallpox in the period supervening immediately upon the development of vaccinia pocks. It seems to me that such evidence can be found.
>
> A final word on this question will be appropriate. If the risks incidental to the production of a negative phase attach, as I believe they do, to prophylactic inoculations in the case of all septicæmic diseases alike, it is obviously incumbent upon us neither to ignore nor to magnify these dangers, and, above all, to recognize that these risks can be minimized. Let it be observed that the risk of

a negative phase comes seriously into consideration only when excessive doses of vaccin are employed, and when the prophylactic inoculations are undertaken in the actual presence of infection. The remedy lies at hand. It lies in the case where a sterilized bacterial culture is employed in the reduction of the dose. It lies in the case of anti-smallpox vaccination in the reduction of the number of insertions; in other words, in limiting the elaboration of the toxins by diminishing the area of skin surface employed for the culture of the organism of vaccinia.

We see that in Wright's opinion the negative phase is not necessarily associated with every immunization process but is due to avoidable causes, *i. e.*, to excessive dosage. In another place he states that "where a dose of vaccin which is only just sufficient to produce an effect on the blood is administered the negative phase is elided and there is registered only a positive phase."

In the preface [13] he again made the following rather characteristic statement:

When once it had become clear in the course of an investigation into the effect of anti-typhoid inoculation upon the blood, that it would be practicable to *control* the "negative phase" and to confer upon a patient the advantages of immunization without risk or appreciable delay, the thought lay very near that it might prove possible to elicit even after microbes had made good their entry into the body, an immunizing response which would be therapeutically valuable.

I might quote further, if space permitted, from Wright to show that while we should not ignore, neither should we magnify the danger of the negative phase.

I would not take so much of your time in considering the various aspects of the negative phase had it not proven the greatest obstacle to our progress in immunizing the army. As you may know, we have very little typhoid in the service in time of peace. In 1908, the last year for which statistics are available, the admission rate was 294 per 100,000 strength, with a death rate of 23 against a death rate of 52.3 (1906) for Washington, and 34.3 (1906) for Baltimore. The death rate in the army is a little less than half that among the civil population of military age in the registration area of the United States.

The time when officers and men begin to inquire about the benefits of vaccination is after a case or two has occurred or a small company epidemic has broken out. The medical officer is appealed to and he very probably looks up the subject and finds that if he proceeds to immunize the command he will be proceeding contrary to the advice of many authorities. After the epidemic is over and the danger past no one is then interested in the subject and it is dropped.

It will, therefore, be worth while to look upon this problem from another point of view, the experimental one.

R. Pfeiffer, in 1908, summed up our knowledge of the negative phase as follows:

The existence of the so-called negative phase is of considerable importance in the question of protective inoculation against typhoid. The existence of this condition was first asserted by Wright and said to consist in a heightened susceptibility to infection among the inoculated, which begins immediately after injection and lasts until the beginning of the immunity reaction.

This negative phase of Wright's has played a great part in the literature of anti-typhoid inoculation in late years, and it, more than anything else, is to be charged with the reluctance to take up the practical carrying out of inoculations in spite of the undeniable results which are obtained when the practice is carried out in the proper way.

It is really rather remarkable that thorough experimental work on this subject hardly exists. We have before us only the work of Wright and his students, whose method cannot be said to be wholly unobjectionable since it is based principally on the so-called opsonic effect of the serum, whose importance in the production of immunity is not yet really cleared up, and which, therefore, is hardly sufficient grounds upon which to base such very important conclusions.

In the immunization of animals to various toxins it not seldom occurs that as a result of the inoculation of the poison there is a temporary sinking in the curve which represents the variation in the antitoxic titer of the serum, and this has been designated as a negative phase; but it has been very wrongly so-called, since a fall below the normal strength of the serum is not observed which would correspond to a condition of heightened susceptibility as contrasted with the normal. The same criticism might be made of the statement of Kutscher and Hetch, that after the second inoculation the bacteriolytic titer of the serum fell below that produced by the first inoculation; finally, certain clinical observations have been brought forward to prove the existence of the so-called negative phase: Men have been taken sick with an especially severe form of typhoid fever immediately after the inoculation of an anti-typhoid vaccin. There are, however, not a very great number of such cases, so that in drawing conclusions from them a certain amount of caution is necessary.

Theoretically the acceptance of a negative phase is an almost self-evident consequence of the well-known Ehrlich side chain theory.

Really a certain number of the protective bodies present in the normal serum must be anchored at least temporarily in satisfying the receptors of the vaccin which is injected, and so cause a sinking of the bactericidal titer of the serum to appear. The only question is whether this fall with the amount of the vaccin which is used in actual practice is sufficient to call forth a distinct increase in susceptibility to infection. It is known from the investigations of Pfeiffer and Friedberger that in bacteriolysis the amboceptors which are anchored at the beginning of the process, soon become free and again able to combine, that is, they are cut out of the circuit for a short time only. On the other hand, the quantitative relations of the amount of bacterial substance which it is practicable to inject into a man in the shape of a vaccin to the anti-bodies which are normally present in the body, are not such as to occupy any great number of them; so that the temporary anchoring of a certain portion of these anti-bodies by the small quantity of vaccin used would be quite insignificant in comparison to the entire quantity of anti-bodies present in the body. This explanation applies even more forcibly to men who already have an increased immunity due to a previous inoculation when they are subjected to a second dose than it does to normal men. The questions which are here raised are suitable for experimental proof only to a certain degree.

Since 1898, R. Pfeiffer and Marx have followed, by means of approved methods, the changes in the blood serum of rabbits which had received subcutaneously relatively large doses (several cultures) of killed cholera germs. In these experiments a fall in the amount of protective bodies already present in the normal serum has never been observed; on the contrary, there has often been observed even in the first 24 or 48 hours a certain, though small rise, which is brought about by the specific irritation acting on the blood-forming organs so that they begin to pour out the

corresponding secretion. These facts have not been sufficiently considered by the adherents of the negative phase. Quite lately I have, together with Friedberger, attacked this problem. In some experiments which have not yet been published we have completely convinced ourselves that guinea-pigs, which had received under the skin of the back relatively large doses of killed typhoid cultures (doses which reckoned according to the body weight were many hundred times the quantity of vaccin used to immunize men) did not show a diminished resistance to intra peritoneal infection with living typhoid bacteria, but on the contrary showed a distinctly increased resistance, and indeed this increase in resistance appeared within a few hours and was demonstrable up to the moment when, as we know, a secretion of specific amboceptors begins.

In these unequivocal experiments there was, therefore, not the slightest indication of a negative phase. One is reminded of the older experiments of R. Pfeiffer and Isaeff, which led to the conception of a condition of (non-specific) resistance as contrasted to a condition of true (specific) immunity.

In our newer experiments a non-specific resistance which arises as a result of the injection of typhoid culture, plays the principal part in protecting the animal, and this is made quite clear from the fact that the guinea-pigs which had been treated with typhoid were at the same time made more resistant to infection with cholera and *vice versa*. I do not desire to apply these results obtained with animals, without further experimentation directly to mankind, but taking all these things into consideration one must wish before accepting the existence and the significance of the negative phase in mankind, that further experimental data be brought forward.

Emery summarizes the work of Pfeiffer and Friedberger as follows:

They conclude that the fear of a negative phase is exaggerated; and it must not be forgotten that the essence of the "opsonin therapy" consists in administering a dose of vaccin, in the first instance, while the index is low.

There is thus no direct proof that the period of the negative phase is coincident with the period of hypersensitiveness to infection. And when we compare it with the period of increased sensitiveness to toxins we find that whereas the negative phase comes on almost immediately, the hypersensitiveness to toxins or tuberculin, or anaphylaxis to serum, takes some days to develop.

In prophylactic vaccination against cholera we hear nothing of any increase of susceptibility following this immunization. Murata[16] has reported its use in a very wide spread epidemic of the disease in Japan in 1902. There were 1299 cases and 902 deaths, 73.3 per cent. The epidemic began on the 31st of July and lasted until December 23. The vaccination was begun on August 5, that is, within a few days of the beginning of the outbreak and during the progress of the epidemic 77,907 persons were vaccinated; among these there were only six cases per 10,000 while there were 13 or over twice as many among the unvaccinated. Murata does not even mention the negative phase in his report.

It is noteworthy that 10 years' experience with anti-plague vaccination[17] has shown that there is no basis in fact for the hypothesis suggested by Sir A. E. Wright, that a negative phase or period of increased susceptibility might follow the vaccination, and that experience has shown that individuals can be vaccinated on the appearance of an epidemic or at any time during its course, and that the vaccination not only does not predispose to infection, but if given during the incubation period actually mitigates the disease.

It is hardly necessary to do more than mention Wright's views as to a negative phase after vaccination against smallpox to dispose of the question. The contrary view is too firmly established to be shaken.

Victor Vaughan, of Ann Arbor, has informed me that his results have been quite similar to those of Pfeiffer, and that his animals are not more susceptible but more resistant to infection immediately after vaccination.

Col. Leishman[18] informs me that the negative phase in anti-typhoid vaccination is a negligible factor.

During the last two years a considerable number of cases of typhoid fever have been treated with vaccins, and although the therapeutic value of the measure has not been determined, we have at least found out that it does no harm, and that clinically no negative phase follows the giving of vaccins.

Since the introduction of vaccination in the army we have had 135 cases of typhoid among approximately 75,000 men, and only one of these was in a man who had been vaccinated. He received the first dose in New York and left next day for San Francisco. The second dose was received 10 days later at sea. On the 19th day after the first dose he was taken into hospital with typhoid. Infection probably occurred between the administration of the first and second doses while crossing the continent. He ran a mild course, the temperature reached 103° F. once only, and there was no relapse. One other case developed on the same transport in a man who had not been inoculated.

With this exception there have been no cases among the 1400 people immunized.

The procedure has been introduced so recently that it is not yet possible to form any idea of the amount or the duration of the immunity from statistics.

There has been no opposition from the laity and it is felt that anti-typhoid vaccination in the army has successfully passed the introductory stage, and that its use should be rapidly extending among all those whose vocation exposes them to the possibility of typhoid infection.

The following conclusions on this subject seem to be justified:

1. Vaccination against typhoid undoubtedly protects to a very great extent against the disease.
2. It is an indispensable adjunct to other prophylaxis among troops and others exposed to infection.
3. It is very doubtful if there is an increase of susceptibility following inoculation.
4. Vaccination during the disease, for therapeutic purposes, fails to reveal any evidence of a negative phase.
5. The statement that vaccination should not be carried out in the presence of an epidemic is not justified by the facts at hand.
6. The procedure is easily carried out and only exceptionally does it provoke severe general reactions.
7. No untoward results have occurred in this series of 3640 vaccinations.

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NOTES ON NEW BOOKS.

A Manual of Operative Surgery. By Sir Frederick Treves, Bart., F. R. C. S., etc., and Jonathan Hutchinson, F. R. C. S. Third Edition. Vol. I. 745 pages. (*Philadelphia: Lea & Febiger, 1909.*)

Sir Frederick Treves, in the preface to the first edition of his Manual published in 1891, defines its scope in the following words: "The present work concerns itself solely with the practical aspects of treatment by operation, with the technical details of operative surgery, and with such part of the surgeon's work as comes within the limits of a handicraft. . . . . For the selection of particular methods of operating I must hold myself answerable. . . . . I have selected such measures as have appeared to me to be the best, and have made no attempt at encyclopædic completeness."

The work, therefore, derives its chief value from being a faithful statement of the surgical practices of one of the most eminent of English surgeons. The present edition to a certain extent lacks this personal quality, for the editor, Mr. Jonathan Hutchinson, states that "So many additions and alterations have been made in this edition that it is really a new work," and further that "The sections on ovariotomy and hysterectomy have been revised by Dr. H. Russell Andrews, those referring to renal and vesical operations have been revised and extensively altered by Mr. F. S. Kidd and myself, the section dealing with operations on the rectum has been revised and largely rewritten by Mr. A. J. Walton."

The volume covers the fields of abdominal, including gynecological, genito-urinary and rectal surgery. It is written in a very concise and pleasing style and is very easy reading. Wise maxims and bits of good advice abound on every page. The following are examples: "In the handling of a sharp instrument in connection with the human body a confusion of the intellect is worse than chorea." "The actual manipulative part of surgery requires no very great skill, and many an artisan shows infinitely more adeptness in his daily work." "There is no doubt that the fewer the implements to which a surgeon accustoms himself, and the simpler they are, the better." "The surgeon who cannot excise the vermiform appendix without inventing a clamp for the purpose has mistaken his vocation."

It is not the purpose of this review to discuss the wisdom of the various procedures advised in the book. We take it to be a fair statement of the best and most conservative British practice. The writers are frankly dogmatic in statement and make no pretense of giving an extensive review of the literature. It is, therefore, unfair to criticise them adversely for not giving any account at all of many operations which are favorably regarded in this country. Thus Finney's pyloroplasty is disposed of in the following sentence: "The very elaborate plastic operation on the pylorus devised by Finney, an American surgeon, appears to us hardly to require description here." It is their misfortune not to be better acquainted with this admirable operation.

One would think from reading this book that the English surgeon is far more cautious than the American. Two noteworthy instances of this are the very elaborate method for cleaning the skin before operation, and the extreme length of time it is advised to keep patients in bed after operation.

When the writer of such a book as this does refer to the practice of clinics other than his own he is in duty bound to have his statement fair and up-to-date. This the writers of the present work certainly do not always do. In speaking of hernia, they describe as the practice at the Johns Hopkins Hospital an operation which has now not been performed here in many years. The book, on the whole, is very interesting and instructive reading.

W. D. G.

Atlas of External Diseases of the Eye for Physicians and Students. By Dr. Richard Greef. Only authorized English translation by P. W. Shedd, M. D. (*New York: Rebman Company, 1906.*)

No more beautiful and accurate plates ever appeared in any medical atlas than in this atlas of external diseases of the eye by Professor Greef, of the University of Berlin, and the text accompanying the plates is characterized by its simplicity and directness and the therapeutic suggestions are all valuable and can be conscientiously followed. We find much more valuable subject matter than we could reasonably expect in an atlas, and this book will no doubt be a welcome addition to an oculist's library. A good deal more care should have been exercised by the translator in rendering such a valuable work into English and the loose use of the word "eyes" where "lids" are evidently intended, on p. 20, should not have occurred, nor the use of the word "disinfectant" for "antiseptic" on p. 55. We do not like such expressions as "bacillary content"; "inobtrusive treatment"; "treated medicamentally," p. 66; "a wave of pus," p. 74; "superficial morbidity," p. 79; "necrotogenic," p. 79, etc., etc., etc. Yet the author is not at fault, and he presents the medical profession a very excellent and valuable atlas.

B. B. Browne, Jr.

A System of Syphilis. Edited by D'Arcy Power, M. B. Oxen, F. R. C. S., and J. Keogh Murphy, M. D., F. R. C. S. With an introduction by Sir Jonathan Hutchinson, F. R. S. Vol. III. (*London: Henry Frowde and Hodder & Stoughton, 1909.*) *Oxford Medical Publications.*

For this volume Professor Osler and Dr. A. G. Gibson have contributed an excellent chapter on "Visceral Syphilis," one of the most thorough in the English language, and admirably illustrated.

"The Clinical Aspects of General Paralysis" is discussed by Dr. Charles A. Mercier, who lays stress on the close relationship of general paralysis and syphilis; all may not agree with him in his views, but none but will be benefited by reading this clear presentation of the question. "Yaws" is described by Professor Aldo Castellani; and, after reading his paper and studying his illustrations, it is hard to believe that the disease has any connection with syphilis. His photographs are splendid, and his description of the disease illuminating. Dr. Stanley B. Atkinson writes on "Some Medico-Legal Associations of Syphilis," and Dr. E. M. Brockbank on "Syphilis and Life Assurance," both valuable papers. The final article is "The Serum Diagnosis of Syphilis," by Dr. Haldin Davis, who gives a full and comprehensive account of the latest work done along this line. All the papers are important contributions, and if the editors succeed as well with the following volumes, the system will be of lasting value.

International Clinics. Edited by W. T. Longcope, M. D. Vol. IV. Nineteenth series. 1909. (*Philadelphia and London: J. B. Lippincott Company.*)

This volume contains a number of timely and well prepared clinical papers on a variety of subjects. It opens with one by Flexner, on "Antimeningitis Serum and the Results of Its Employment." No one is more competent than the author to speak authoritatively on this subject; and to foreigners what he says should prove especially interesting. Charles Green Cumston describes fully "Epiploitis Following the Radical Cure of Hernia," a condition not often recognized by the surgeon; and there are various other papers to appeal to workers in different lines.

Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India. New Series No. 36. Observations on Rabies, with Especial Reference to an Atrophic Form of the Disease Occurring in Animals. By Major G. Lamb, M. D., I. M. S., and Captain A. G. McKendrick, M. B., I. M. S. Price 9 pence. (*Calcutta: Superintendent Government Printing, India, 1909.*)

This is a brief but carefully prepared report. It describes the passage of the virus of the street through the dog; a peculiar form of rabies seen in rabbits and dogs; the susceptibility of various animals toward fixed rabbit virus; an attempt to immunize monkeys by means of single doses of fixed rabbit virus injected subcutaneously; bactericidal properties of the serum of patients taken both during the course of anti-rabic inoculations and after the treatment had been completed; and protocols. Students interested in the study of rabies should give careful attention to this report.

Practical Points in the Use of X-ray and High-Frequency Currents. By Aspinwall Judd, M. D., etc. (*New York: Rebman Company, 1909.*)

As the author states in his preface, this book is intended for the general practitioner and no attempt has been made at absolute scientific accuracy.

Part I is devoted entirely to descriptions of apparatus and use of the same. This section is to be especially commended as the author describes in detail individual parts of X-ray apparatus and how properly to use them, a subject which is too frequently curtailed in most text-books.

The beginner, by carefully studying this section, will find many valuable hints which will save him much useless worry and even damage of apparatus.

Part II is devoted to radiotherapy and to the therapeutics of high-frequency currents. The author in a brief manner outlines the diseases to which these treatments can be applied. In his endeavors to be brief he has sacrificed some of the details which to the reader seem essential.

Manual of Operative Surgery. By H. J. Waring, M. S., M. B., B. Sc. (Lond.), F. R. C. S. Third Edition. 750 pages. (*London: Henry Frowde and Hodder & Stoughton, 1909.*) *Oxford University Press.*

The first edition of this Manual appeared in 1898. It was "written with the object of serving as a text-book for the classes held in the Operative Surgery Department of St. Bartholomew's Hospital." The work has apparently been very popular in the English medical schools, as it has been through three editions in 11 years. The author has compressed a great amount of information into his book, which covers the entire field of operative surgery, even ophthalmic operations being included. The subjects of general surgical technique, and the sources of wound infection are also discussed. The style is concise and categorical. It is illustrated with 521 figures, several of which are in color. Many of these are from standard works in special departments of surgery. The book is convenient and not too bulky and deserves a wide-spread popularity.

W. D. G.

Progressive Medicine. Vol. IV. December, 1909. (*Philadelphia and New York: Lea & Febiger.*)

The volume contains chapters on "Diseases of the Digestive Tract," "Genito-Urinary Diseases," "Surgery of the Extremities," "Diseases of Kidneys and Therapeutics," respectively contributed by Edsall, Belfield, Bloodgood, John Rose Bradford of England, and Landis. It is only necessary to note the appearance of the work which is published quarterly and to whose merits attention has frequently been called.

Surgery. Its Principles and Practice. Volume V. Edited by W. W. Keen, M. D., LL. D., Hon. F. C. R. S., Eng. and Edin., etc. Per volume, $7.00 net. (*Philadelphia and London: W. B. Saunders Company, 1909.*)

With this volume this new practice ends, and Dr. W. W. Keen deserves the thanks of the profession for having secured for them this useful work, which for some years to come will be regarded as the standard in the English language, at least by American surgeons. A quarter of this volume is devoted to the "Surgery of the Vascular System," by Rudolph Matas; no better authority could have been selected for the work and as a result the chapter is one of the very best in the entire system and one of the best in the language. That on the "Surgery of the Female Genito-Urinary Organs" is less good, and its bibliography shows a very limited reading on this important subject. These two chapters fill nearly half the book, and the other half is given over to a number of subjects which should have appeared in earlier volumes, but unfortunately were late in coming to the hands of the editor. This gives the volume a rather heterogeneous and padded aspect; it would have been better for the omission of one or two of the chapters. If there is a call for a second edition of this Surgery, it is to be hoped that some one person will be employed to edit the bibliographies which follow the chapters, so that one correct system of abbreviation may be used throughout. Foreign titles are wrongly spelled, capitalized and accented, not to speak of a variety of abbreviations of one word which are startling; for instance, "Chirurgie" appears in this form and in four others—"Chir.," "Chirg.," "Chirur.," and "Chirurg"; "Beiträge," "Beit.," "Beitrag.," and "Beiträg" all occur; and there are many others, as "Deut." and "Deutsch"; "Woch" and "Wochen"; "Arch." and "Archiv"; "Berl." and "Berlin," etc. In a classical work published by a leading house attention should be paid to this detail, for typographical errors are as important to the credit of the work here as in the text.

A Text-book of Experimental Physiology for Students of Medicine. By N. H. ALCOCK, M. D., D. Sc., and F. O'B. ELLISON, M. D. With a preface by E. H. STARLING, M. D., F. R. C. P., F. R. S. Price, $1.50. (*Philadelphia: P. Blakiston's Son & Co., 1909.*)

"In the revised regulations of the University of London, a syllabus of practical physiology has been prescribed, which is more in accordance with the actual requirements of the student of medicine. The present work is an attempt to put this syllabus into practice." These words taken from the preface by Dr. Starling explain the object of this work, and as he goes on to give his approval of this set of problems, the quality of the work is vouchsafed for, although some teachers would doubtless select other experiments. In this small book there are four lessons on muscle, eleven on circulation, three on digestion, four on respiration, two each on the blood and urine, one on temperature, four on the nervous system, and six on special senses. It is intended for "practical classwork," and if the student masters the principles of these experiments, he will be able to comprehend and treat disease intelligently.

Visiting Nursing in the United States. Containing a Directory of the Organizations Employing Trained Visiting Nurses, with Chapters on the Principles, Organization and Methods of Administration of Such Work. By YSSABELLA WATERS, Henry Street (Nurses') Settlement, New York City. (*New York: Charities Publication Committee, 1909.*)

The directory is issued to show what is being done by trained nurses in every department of social service and philanthropic activity. The author wisely points out the correct principles which underlie this movement, "Purity of motives, integrity of work and broad social conceptions of duty to mankind are . . . . necessary qualities in satisfactorily carrying out the daily routine." She further adds that "visiting nurse associations emphasize the importance of a work organized distinctly for the purpose of supplying trained nurses to give home care to the sick poor and to those of small means." How well this purpose has been put into practical form is shown by the statement that in August, 1909, there were 566 such associations in the United States with 1413 nurses. To those persons who contemplate the establishment of similar organizations in future this volume will be indispensable.

The directory which follows is very carefully compiled and furnishes all the information needed to answer any inquiry in reference to the various societies. The book is a very creditable example of what the trained nurse can do in the line of book-making. It is a useful manual for the guidance of all who are planning similar associations in the city or country.

A Handbook of Medical Diagnosis. For the Use of Practitioners and Students. By J. C. WILSON, A. M., M. D., Professor of the Practice of Medicine and Clinical Medicine in the Jefferson Medical College, etc. Illustrated. (*Philadelphia and London: J. B. Lippincott & Co., 1909.*)

This is a voluminous work and contains a large amount of useful information. Some parts might have been omitted, however, without impairing its value, as it is overburdened with detail. The manner of presentation is not novel, and some of the latest work is not referred to, even though otherwise very comprehensive. Thus in discussing tabes and general paresis no reference is found to two points of great practical importance; the occurrence of a positive Wassermann reaction and the characteristic changes in the spinal fluid. The book is profusely illustrated, and should be useful to those who desire general rather than particular information on the subjects treated.

P. W. C.

A Practical Treatise on Ophthalmology. By L. WEBSTER FOX, M. D., LL. D., etc. Illustrated. (*New York and London: D. Appleton & Co., 1910.*)

This is another text-book on ophthalmology, but just what "call" the author heard when he concluded to issue to the medical profession and students this volume has not been ascertained by the reviewer after rather careful perusal. Most of the matter contained therein is presented in more authoritative and convincing form in several other American text-books, and the author has failed to vitalize the book by a sane and definite system of therapeutics. Like to the man overboard, to whom is thrown numerous articles by which he might save himself, so the author offers at random, numerous suggestions from which the reader may possibly select the right ones to treat the patient safely and judiciously. On the other hand he may find to his and to the patient's regret that he made the wrong selection. On practically every subject the author gives evidence that he has not reached a stage of mental tranquility and equipoise as regards the therapeutic measures which he himself prefers and adopts, and the result is that the reader is left in doubt.

Again many of the therapeutic measures which he advocates we do not approve of. For instance, we would not think of advising corrosive sublimate irrigations in such strength as (1-2000) in gonorrhœal ophthalmia; for such a strength would tend to injure and macerate the corneal epithelium, which is already subject to injury by the gonorrhœal pus. In the same disease we would not use eserine if the cornea should become steamy, as the author says he has done during the last few years, nor do we use cold compresses, but we do advocate *the very* frequent *irrigations* with boracic acid in warm water which the author does not emphasize at all in his apparent anxiety to do something with lotions containing *six* ingredients *applied* on cotton pledgets. The author states that in gonorrhœal conjunctivitis the inflammation and œdema may be reduced by . . . . or by incisions of the lids at the outer canthus (p. 145) to relieve pressure on the eyeballs.

We consider it a very serious omission, when he failed to add that this would practically never be necessary. If we continued to call attention to therapeutic suggestions which we do not approve of we would practically have to rewrite the Therapeusis of the entire book, so we will say that we do not approve of salt-injections in iritis, nor calomel dusted on phlyctenular ulcers, nor the use of peppermint water or of quinine in "eye" washes (p. 144), or of rose-water (which is usually kept on hand so long in most drug-shops that it is turbid with bacteria or fungus growth). Considerable fault is to be found with the book in that so many preparations are recommended which are not recognized by the U. S. P., *vide* Boroglyerid, pp. 157, 164, Chinosol, p. 158, Chloretone, Cerevisine. The reviewer believes that ophthalmology can be practiced with splendid success without those preparations which are subject to change in composition at the whim of the manufacturing pharmacist, and which the average druggist does not have sufficient demands for, to warrant him carrying fresh in stock.

There is an unfortunate error in regard to the trial-frame on p. 640, and the remarks made regarding the taking of measurements for spectacles are almost foolish. The dogmatic assertions that "when phlyctenular conjunctivitis is met with in adults there is always a history of ocular involvement in childhood," p. 153, and on p. 238, "In episcleritis the iris is always discolored and sluggish, although no iritis is demonstrated," and on p. 241, "In scleritis there is *marked impairment* of vision," suggest the surprising and "wild" answers seen on some student's examination papers, and we should hardly expect them, set down in cold type, in a "Practical Treatise on Ophthalmology"

published by the professor of eye diseases at a large medical educational institution.

These, then, are some of the faults, and while "the" book is readable, there are no special virtues. As far as the students are concerned, several smaller books cover the field more satisfactorily, and as for the medical men and ophthalmologists, they can dig in the gold mines of four or five text-books of ophthalmology for themselves, with Gray's Anatomy and a good Pathology by their side.

B. B. Browne, Jr.

Infectious Diseases. A Practical Text-book. By Claude Buchanan Ker, M. D. Ed., F. R. C. P. Ed., etc. (*London: Henry Frowde and Hodder & Stoughton, 1909.*) *Oxford Medical Publications.*

The title of this work is exact, it is distinctly practical; and the book itself a most excellent guide. The diseases selected and described by the author are those treated in the City Hospital in Edinburgh, of which he is in charge. They are measles, rubella, scarlet fever, small-pox, vaccinia, chicken-pox, typhus fever, relapsing fever, enteric fever, diphtheria, erysipelas, whooping-cough, mumps, and cerebrospinal meningitis. This is without doubt one of the best of the new Oxford Medical Publications, and a work which should have a large sale. Few can write with more authority then Dr. Ker, and there is no better book on this group of diseases in the English language. The author's style is delightful; he is master of the true "clinical" method of instruction, and his work shows the results of long years of experience and thought. His judgment is sound, as is well marked in his treatment, but each division of his subject is handled with a master's skill. This work should be in the hands of every general practitioner and is suited to American conditions as well as to those of Great Britain. It is thoroughly up-to-date, and the illustrations are as good as can be found. All in all, it is a first-class work, and ranks with the very best. It is a rare pleasure amongst the immense amount of commonplace work to find a book which is preeminent in quality.

BOOKS RECEIVED.

Progressive Medicine. A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Edited by Hobart Amory Hare, M. D., assisted by H. R. M. Landis, M. D. Volume IV. December, 1909. 8vo. 334 pages. Lea & Febiger, Philadelphia and New York.

United States Department of Agriculture. Twenty-fourth Annual Report of the Bureau of Animal Industry. For the year 1907. 8vo. 486 pages. 1909. Government Printing Office, Washington, D. C.

St. Luke's Hospital. Medical and Surgical Reports. Volume I. For 1908 and 1909. Edited for the Medical Board by Austin W. Hollis, M. D. 1909. 8vo. 225 pages. New York.

A Practical Treatise on Ophthalmology. By L. Webster Fox, M. D., LL. D. With six colored plates and three hundred illustrations in text. 1910. 8°. 807 pages. D Appleton & Co., New York and London.

Modern Clinical Medicine. Diseases of Children. Edited by Abraham Jacobi, M. D., LL. D. An Authorized Translation from "Die Deutsche Klinik" under the General Editorial Supervision of Julius L. Salinger, M. D. With 34 illustrations in the text. 1910. 8vo. 828 pages. D. Appleton & Co., New York and London.

The British Guiana Medical Annual. Sixteenth Year of Issue. 1908. Edited by K. S. Wise, M. B., B. S., B. Sc. (Lond. Univ.), M. R. C. S. (Eng.), L. R. C. P. (Lond.) 1909. 8vo. LII + 126 pages. Printed by "The Argosy" Company, Limited, Demerara.

Scientific Memoirs. No. 36. (New Series.) By Officers of the Medical and Sanitary Departments of the Government of India. Observations on Rabies: With Special Reference to an Atrophic Form of the Disease Occurring in Animals. By Major G. Lamb, M. D., I. M. S., and Captain A. G. McKendrick, M. B., I. M. S., 1909. Fol. 34 pages. Superintendent Government Printing, Calcutta, India.

A Text-book of Physiology. By William H. Howell, Ph. D., M. D., LL. D. Third edition, thoroughly revised. 1910. 8vo. 998 pages. W. B. Saunders Company, Philadelphia and London.

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CONTENTS.

ON THE OCCURRENCE OF GOITRE (ACTIVE THYROID HYPERPLASIA) IN FISH.[1]

By David Marine, M. D., and C. H. Lenhart, M. D.,
Cleveland, Ohio.

(From the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University.)

Water has been associated with the cause of goitre since the earliest observations and writings on diseases of the thyroid gland. The list of substances that may be present in solution or suspension comprise a great variety of organic and inorganic chemical combinations; also various forms of plant life as algae and bacteria and animal life as protozoa. Of the great variety of chemical substances that have been brought forward as etiological factors the most prominently mentioned have been the sulphides and sulphates of iron, magnesia and calcium and also the carbonates of calcium and magnesia. Of the extensive bacterial analyses conducted by Bircher, Kocher and others, no definite conclusions have been reached. During the past year, McGarrison working with endemic cretinism in the Himalaya mountains has brought forward certain amoebæ as etiological factors.

Summing up our acquaintance with the vast literature dealing with water as a causal factor in goitre, we have been quite unable to convince ourselves that there is any proof that the substances thus far described have any causal connection or even that any direct evidence has been presented that water is a causal factor in goitre.

Inasmuch as most of the land animals in goitrous districts have thyroid changes, it occurred to us that by the examination of fish thyroids in such districts one might get more specific information whether water was or was not a factor in the development of goitre.

In the course of our investigation we have examined moun-

[1] Read at the meeting of the Cleveland Academy of Medicine, December 10, 1909.

tain trout from the Yellowstone Park, from Utah and California; sea trout and sea bass from the Atlantic Ocean; gold fish from local dealers; lake pike, lake herring, white bass,

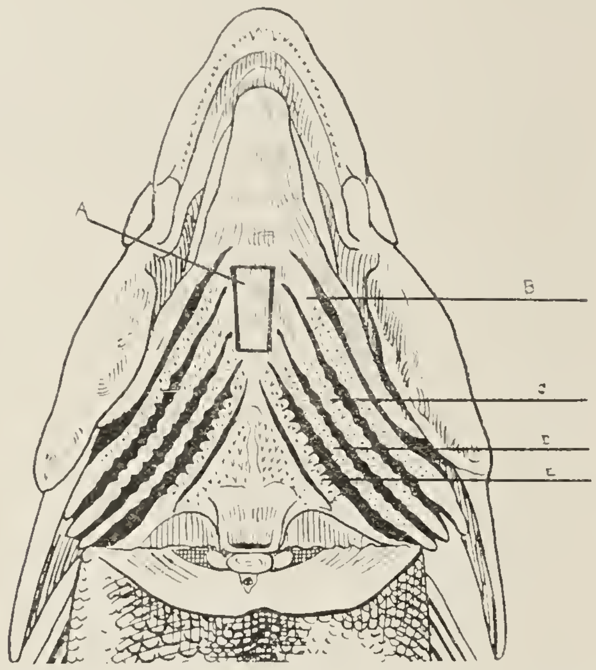

Fig. 1.—Illustrates the location of the thyroid area in the lake pike. It is applicable to bony fish in general. A = thyroid area; B = 1st gill segment; C = 2d gill segment; D = 3d gill segment; E = 4th gill segment.

sheephead and carp from Lake Erie. We have observed goitrous changes only in the fish obtained from Lake Erie.

Fig. 2.—Drawing illustrating distribution of normal thyroid follicles in bony fish as seen in transverse section of the thyroid area. A = pharyngeal mucosa; B = thyroid follicles.

Of the Lake Erie fish, the pike and bass very commonly are affected, while the sheephead and herring are but rarely affected. The carp so far as our observations have extended is not at all affected.

Before describing these goitrous changes in the lake pike and bass it seems appropriate to add a brief account of the normal thyroid gland in the bony fish.

The normal thyroid (Fig. 1) in the several varieties of fish

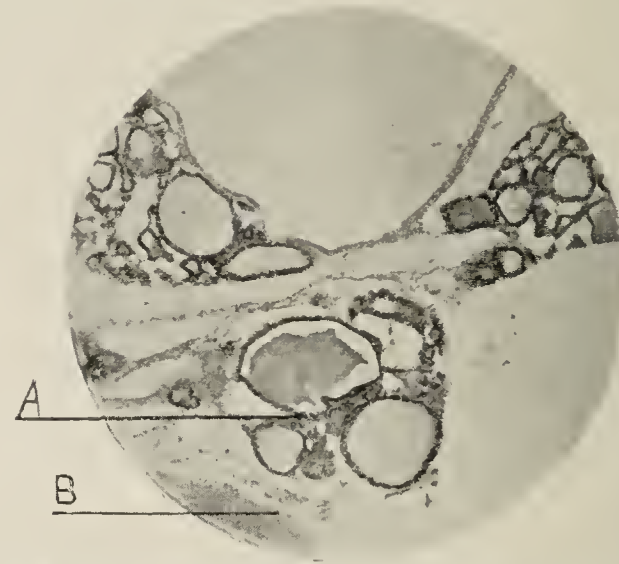

Fig. 3.—Microphotograph illustrating mild degree of thyroid hyperplasia in the lake pike. A = thyroid follicles; B = ventral aorta.

examined shows only minor individual differences and is also strikingly like the normal thyroid of the higher animals. The gland alveoli are loosely distributed about the ventral aorta between the first and third gill segments and extend outward for slight distances on the second and third gill arch arteries. *The gland is not encapsulated* as in reptiles and amphibia.

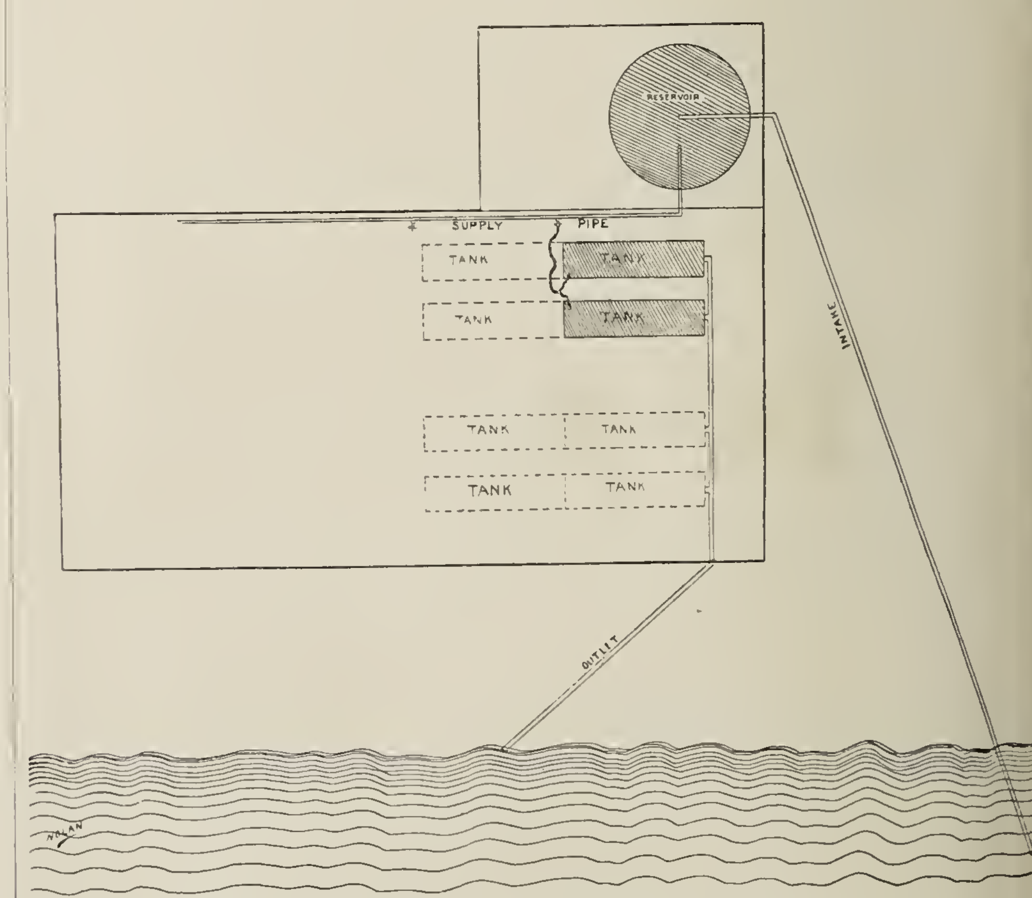

Fig. 4.—Diagram of hatchery showing arrangement of troughs, etc.

The main mass of thyroid lies in the second gill segment and widely scattered alveoli in the alveolar tissue extend antero-posteriorly and laterally from this central mass.

Histologically, the gland is very vascular. Each alveolus is surrounded as in the mammalian gland, with a rich capillary network. The alveoli are rounded and vary in diameter from 0.1-0.5 mm. The size of course depends largely on the age and size of the fish as in other animals. The lining epithelium is low cubical regularly arranged in a single layer with small darkly staining nuclei. The colloid stains uniformly with eosin and comes in direct contact with the lining epithelium. In its general histological appearance therefore, the normal fish thyroid is similar to that of mammals in all its essential characteristics except that there is no capsule (Fig. 2).

In certain Lake Erie fish, as above mentioned, and particularly in the lake pike, we have observed a departure from the normal type above described. This change is similar in all its essential features to the thyroid hyperplasia in mammals as typified by the spontaneous or the induced hyperplasias of dogs or the hyperplasia of exophthalmic goitre in man (Fig. 3).

As in the higher animals so in the fish, there are different degrees of hyperplasia varying from the slightest departure from normal to the marked glandular hyperplasias. The most striking changes are seen in the *blood supply,* in the stainable *colloid* and in the *epithelium.*

The capillaries and larger vessels of the stroma are dilated. The stainable colloid is decreased—but slightly in the early stages while it may be entirely absent in the marked degrees of hyperplasia. The epithelium varies from cubical in the milder degrees to high columnar in the marked degrees of hyperplasia. The infoldings and plications of the lining epithelium are present, though perhaps less marked than in similar degrees of hyperplasia in mammals. This phenomenon just as the suggestive appearance of invasion of the surrounding tissue—bone and muscle—by the hyperplastic gland, is probably due to the lack of a gland capsule and its restraining effect. None of the pike examined has shown thyroid enlargement clinically although it may enlarge so as to be detectable clinically. We have also observed one example of spontaneous colloid goitre in the pike, that is a hyperplasia that has undergone spontaneous recovery just as occurs in the higher animals.

From what we already know of the hyperplasias of the higher animals and from the fact that a similar hyperplasia occurs in fish it could be inferred with practical certainty that spontaneous involution (reversion) of these fish hyperplasias could also occur under favorable conditions of food and environment.

In order to determine whether these thyroid hyperplasias in fish undergo the same kind of involution (reversion) as do the mammalian hyperplasias following the administration of iodin containing substances the following experiment was made:

TABLE 1.—IODIN EXPERIMENT—CONTROLS.

Fish No.	Date taken.	Histological condition of thyroid.		Classification.
		Stainable Colloid.	Epithelium.	
1	Oct. 2	Everywhere present, nearly normal.	High cubical, regular.	Normal-early glandular hyperplasia.
2	" 3	Everywhere present, nearly normal.	High cubical, regular.	Normal-early glandular hyperplasia.
3	" 4	Everywhere present, reduced.	High cubical, regular.	Early glandular hyperplasia, very vascular.
4	" 5	Everywhere present, nearly normal.	High cubical, regular.	Normal-early glandular hyperplasia.
5	" 6	Much reduced, absent from many follicles.	Columnar, regular.	Early-moderate glandular hyperplasia.
6	" 7	Slightly reduced.	High cubical, regular.	Early glandular hyperplasia.
7	" 8	Practically absent.	High columnar, regular.	Moderate glandular hyperplasia.
8	" 9	Present everywhere in follicles, nearly normal.	High cubical, regular.	Normal-early glandular hyperplasia.
9	" 10	Present throughout, reduced.	High cubical, regular.	Early glandular hyperplasia.
10	" 11	Present throughout, reduced.	High cubical, regular.	Early glandular hyperplasia.
11	" 12	Absent.	High columnar, regular.	Moderate-marked glandular hyperplasia.
12	" 13	Present throughout, slightly reduced.	High cubical, regular.	Early glandular hyperplasia.
13	" 14	Absent.	High columnar, regular.	Marked glandular hyperplasia, generalized fibrosis of thyroid area.
14	" 15	Absent.	High columnar, regular.	Marked glandular hyperplasia, well-marked infoldings and plications.
15	" 16	Everywhere present, nearly normal.	Cubical, regular.	Normal thyroid(?) (normal-early glandular hyperplasia).
16	" 17	Absent.	High columnar, regular.	Marked glandular hyperplasia.
17	" 18	Reduced, absent in some follicles.	Columnar, regular.	Early-moderate glandular hyperplasia.
18	" 19	Reduced in all, absent in many follicles.	High columnar, regular.	Moderate glandular hyperplasia.
19	" 20	Reduced.	Columnar, regular.	Early-moderate glandular hyperplasia.
20	" 21	Reduced.	High columnar, regular.	Moderate glandular hyperplasia.

Forty-two healthy pike, varying from 30-35 cm. in length, were transferred directly from a Lake Erie pound net to the State Fish Hatchery at Put-in-Bay. Twenty fish were placed in the control trough and twenty-two fish in the trough to which iodin was added daily. These troughs were of the same size (Fig. 4)—their inside measurements being 168 x 31 x 20 inches with 60 cu. ft. capacity. Lake Erie water was supplied to each trough in equal amounts from the reservoir. The inflows were adjusted so as to fill the troughs in eight hours. One cubic centimeter of Lugol's solution (1 gm. iodin, 2 gm. KI., 300 cc. water) was added daily to the contents of one of the troughs. One fish daily was removed from each of the troughs for histological examination. The results of these histological examinations are presented in Tables No. 1 and 2.

By comparing these tables it is seen that the control fishes' thyroids, while exhibiting wide variations in their histological appearance, do not tend to return to the colloid or resting

stage. On the other hand in the fish exposed to the small amounts of iodin from one to twenty-five days, the thyroids do react and return to the colloid or quiescent state. These fish hyperplasias, therefore, react in the same manner with iodin as do the hyperplasias of mammals, viz., the return of the hyperplasias to the colloid or quiescent state and as has been shown for mammals this is the nearest normal condition that thyroids can assume which have once been the seat of active hyperplasias.

These observations are perhaps the most direct evidence that water is in some way (still unknown) associated with the development of goitre. Our observations are still too few to allow of any general statements, although it may be stated that carnivorous fish just as carnivorous mammals are more frequently affected as is shown in the great frequency of these changes in pike and their absence in carp. On the other hand, the two examples of ocean carnivora examined did not show these hyperplastic changes.

TABLE 2.—IODIN EXPERIMENT—EFFECT OF ADMINISTRATION OF IODIN.

Fish No.	Date taken.	Duration of iodin administration.	Histological condition of thyroid.		Classification.
			Stainable colloid.	Epithelium.	
1	Oct. 3	1 day.	Practically normal.	Cubical, regular.	Normal thyroid(?)(normal-early glandular hyperplasia).
2	" 4	2 days.	Present throughout, slightly reduced.	High cubical, regular.	Early glandular hyperplasia.
3	" 5	3 "	Nearly absent.	High columnar, regular.	Moderate glandular hyperplasia, generalized fibrosis of thyroid area.
4	" 6	4 "	Present throughout, somewhat reduced.	Cubical, regular.	Colloid-early glandular hyperplasia, involuting (reverting).
5	" 7	5 "	Present throughout.	Cubical, regular.	Normal-early glandular hyperplasia.
6	" 8	6 "	Present throughout, nearly normal.	Cubical, regular.	Colloid-early glandular hyperplasia, involuting (reverting).
7	" 9	7 "	Present throughout, nearly normal.	Cubical, regular.	Colloid-early glandular hyperplasia, involuting (reverting).
8	" 10	8 "	Normal.	Low cubical, regular.	Normal-colloid.
9	" 11	9 "	Slightly reduced.	Cubical, regular.	Colloid-early glandular hyperplasia, involuting (reverting).
10	" 12	10 "	Present throughout, reduced in all follicles.	Columnar, regular.	Colloid-moderate glandular hyperplasia, involuting (reverting).
11	" 13	11 "	Present throughout, reduced in all follicles.	Columnar, regular.	Colloid-moderate glandular hyperplasia, involuting (reverting).
12	" 14	12 "	Normal.	Low cubical, regular.	Colloid goitre(?)(colloid-early glandular hyperplasia), involution nearly complete.
13	" 15	13 "	Present throughout.	Cubical, regular.	Colloid-early glandular hyperplasia.
14	" 16	14 "	Abundant in all follicles.	Low cubical, regular.	Colloid goitre, complete involution (reversion).
15	" 17	15 "	Present in all, somewhat reduced.	Cubical, regular.	Colloid-early-moderate glandular hyperplasia, rapidly involuting (reverting).
16	" 18	16 "	Normal.	Low cubical, regular.	Colloid goitre, generalized fibrosis, complete involution (reversion).
17	" 19	17 "	Normal.	Low cubical, regular.	Normal-colloid, involution from very early degree of hyperplasia if any hyperplasia at all had occurred.
18	" 20	18 "	Normal.	Low cubical, regular.	Normal thyroid, no evidence of any previous hyperplasia, however slight.
19	" 21	19 "	Abundant.	Low cubical, regular.	Colloid goitre, complete reversion.
20	" 23	21 "	Abundant.	Low cubical, regular.	Normal-colloid.
21	" 25	23 "	Abundant.	Low cubical, regular.	Colloid goitre, complete involution (reversion).
22	" 27	25 "	Abundant.	Low cubical, regular.	Colloid goitre, complete involution (reversion).

This experiment also emphasizes two other features which the fish thyroid hyperplasias have in common with mammalian hyperplasias, viz., the small quantities of iodin and the relatively short time necessary to induce these changes. It can be inferred from these anatomical and experimental observations that hyperplasia of fish thyroids are similar in nature to those of mammals and also that probably the stimulus or stimuli producing the thyroid reaction in fish is similar to that acting in mammals.

To sum up then, we would emphasize three points:

(1) That in regions of endemic goitre the fish may also be affected.

(2) That the thyroid hyperplasias of fish react with iodin exactly as do the thyroid hyperplasias of the higher animals.

(3) That the findings of these changes in fish is perhaps the most direct evidence that goitre may be associated with water.

REMARKS MADE UPON THE PRESENTATION OF A PORTRAIT OF DR. FERDINAND EDME CHATARD, TO THE MEDICAL AND CHIRURGICAL FACULTY OF MARYLAND, DECEMBER 8, 1909.

By J. Whitridge Williams,
Professor of Obstetrics, Johns Hopkins University.

Ladies and Gentlemen: It is my privilege this evening, on behalf of the Chatard family, to present to the Baltimore City Medical Society, and through it to the Medical and Chirurgical Faculty of Maryland, the portrait of Dr. Ferdinand Edme Chatard, which stands before you. It was painted by Mr. Robert Hinckly, of Washington, and is thought to give an excellent idea of Dr. Chatard's appearance at the age of seventy.

All of us who are familiar with the medical history of Baltimore know how prominent a position he held for more than fifty years of the last century in our city, in which he was extensively engaged as a general practitioner, but more particularly as an obstetrician. It is particularly on account of the latter fact, I suppose, that I was requested to present his portrait to you; and I assure you that I regard the invitation as a peculiar honor, and shall take the greatest pleasure in telling our younger members something of his life work.

Ferdinand Edme Chatard was born in Baltimore, August 3, 1805, in a house on W. Saratoga Street, opposite to where St. Alphonsus Church now stands. His father, Dr. Peter Chatard, a native of San Domingo, settled here in the year 1800, and was extensively engaged in practice up to the time of his retirement in 1845. The younger Chatard was educated in this city and received the degree of A. B. from Mount St. Mary's College in 1824 and of M. D. from the University of Maryland in 1826. He then studied for three years in Europe, chiefly in Paris, where he had ample opportunity to acquire the facility in obstetrical operations which so characterized his later work. After his return to Baltimore in 1829, he practised medicine for fifty-four years until his retirement in 1883, and five years later, October 18, 1888, died suddenly at the age of eighty-three.

He married Miss Eliza A. Marean, a daughter of Silas Marean, Esq., and was survived by three sons and one daughter. The former were Thomas, Silas and F. E. Chatard Jr., all of whom studied medicine. Thomas, however, did not practise; Silas later entered the ministry and is now the Catholic Bishop of Indianapolis; while Ferdinand Jr., practised medicine in this city until the time of his death in 1900. The only surviving daughter, Juliana, is now a Sister of Charity. One of the sons of Ferdinand Jr., is Dr. J. Albert Chatard, the Secretary of the Book and Journal Club, and one of the younger members of the Faculty, who takes great interest in its affairs.

Thus you see, four generations of this family have been continuously engaged in medical practice in this city from the year 1800 to the present time, a period of one hundred and nine years; so that one may well speak of the Chatard medical dynasty, which with one exception, is the longest in Baltimore. Dr. John N. Mackenzie, the laryngologist, is the representative of the latter, having been preceded by his father, John Carrere; his grandfather, John Pinkerton, and his great grandfather, Colin Mackenzie, who began practice in this city in the year 1797. It is interesting to note that the latter was one of the original physicians to the old Baltimore Hospital, which stood on the site now occupied by the Johns Hopkins Hospital.

As far as I know, only four other families in Baltimore claim so long a medical ancestry, namely, the O'Donovans, the Smiths, the Magruders and my own family, although none of them have practised continuously in this city for the entire period. The accomplished Secretary of the Baltimore City Medical Society, Dr. W. E. Magruder, dates his medical ancestry back to his great grandfather Zadock, who graduated in 1786. His ancestors, however, practised in Montgomery County, Md., and the present Dr. Magruder came to Baltimore in 1895. The other three families have a record of three generations of practitioners in this city and an earlier one elsewhere. My grandfather, Dr. John Whitridge, settled here in 1820, Dr. John Henry O'Donovan in 1824, and Dr. Nathan Ryno Smith in 1827. All of them had sons who were, and grandsons who are at present, engaged in practice in Baltimore; and as far as I can ascertain my own medical ancestry is the longest of all, as my great-grandfather, William Whitridge, began practice in Tiverton, R. I., in 1770—one hundred and thirty nine years ago.

After this genealogical digression, I return to Dr. Chatard, who, after returning from Europe, thanks to his father's influence and his own excellent attainments, soon built up a large practice, and for nearly fifty years was the leading obstetrician among the upper classes of this city. During that period he delivered 5268 private patients, and some idea of his activity may be gained from the fact that during the year 1858 he attended 178 obstetrical patients. His father, Dr. Peter Chatard, also had an extensive obstetrical practice, and in 1855, his son-in-law, Dr. W. C. Van Bibber, reported to the Medical and Chirurgical Faculty a summary of 4309 cases which he had attended. Thus, it appears that during the first three-quarters of the last century these two men delivered nearly 9600 patients, which is the largest private obstetrical practice with which I am familiar, being most nearly approached by the experience of Drs. John and T. E. Beatty, of Dublin, who left a record of 7690 cases.

Dr. Chatard lived for many years at the southwest corner of Charles and Lexington Sts., now occupied by O'Neill's dry goods store. The portrait gives some idea of his appearance, and those who knew him say that his most striking personal characteristic was extreme neatness, which applied not only to his person, but to all his dealings in life. I am told at the time when vaccination was practised from crusts he was frequently

the only physician in town who was sufficiently thoughtful and methodical to carry a supply over the summer, so that the following winter he was able to supply his brother practitioners with sufficient virus for their first vaccinations.

He was extremely sympathetic and kindly, and possessed the confidence of his patients in the highest degree. Only last summer I met an elderly lady on the steamer returning from Europe, who had been his patient for many years, and she stated that she could never forget his kindness to her under most trying circumstances. Like most of the practitioners of his generation he attended closely to business and took very little holiday, and from what I can learn it is probable that an enforced absence from the city in 1845, following an epidemic of puerperal fever, was probably his longest vacation. He was a devout Roman Catholic and all of his descendants have remained in the same faith. He was not a writer, and therefore made no contributions to the medical literature of his time, and were it not for the record of his cases which he left, and which was kindly placed at my disposal by his grandson, I should be able to say comparatively little of his work.

As I have already indicated he attended 5268 private patients in labor and recorded and tabulated his observations in 5182 cases; and it is upon his own data that I shall rely to show how excellent an obstetrician he was.

Thus, he noted the presentation and position of the child in 5171 cases, and the percentages given in the following table show that his conclusions were quite comparable to those in the most recent text-books:

Vertex	4,920	cases,	95.14	per cent.
Breech	181	"	3.52	" "
Face	31	"	0.60	" "
Transverse	29	"	0.56	" "
Compound	9	"	0.17	" "

Twins occurred once in 85 labors and triplets were delivered once in the entire series. The greatest average number of births occurred in December and the smallest number in April, and it is interesting to note that his father, Peter, had exactly the same experience. Fifty-two per cent of his children were boys and 48 per cent girls, a proportion of 108 to 100, a very close approach to the results shown by world-wide statistics.

That he was a close and accurate observer is also shown by the results which he obtained by tabulating the time of birth in 4484 cases. This was between 6 a. m. and 6 p. m. in 2256 instances, and between 6 p. m. and 6 a. m. in 2228 instances—50.3 per cent and 49.7 per cent, respectively, a difference of 0.6 per cent in favor of the daylight twelve hours. Such a conclusion is contrary to the general opinion, as it is usually believed that many more labors occur at night; but its correctness is borne out by my own experience, which shows that only two per cent more births were noted in the night than in the day twelve hours.

He made no note concerning the weight of the children, but I imagine that his results were very similar to those of his father, who stated that in his experience only one child had weighed as much as twelve and only five as much as eleven pounds; thus showing that he must have weighed the children accurately instead of attempting to please the parents by guessing at their weight.

On considering his results we find that they were extremely favorable for the period in which he practised, as he lost only thirty-nine mothers from the following causes: Hæmorrhage 3, placenta prævia 4, ruptured uterus 5, eclampsia 8, and infection 19. This corresponds to one death in 133 cases or a mortality of 0.75 per cent, and is a distinct advance upon the normal mortality of 1 to 120 as calculated by Matthews Duncan in his monograph on "The Maternity in Child-bed," published in 1879.

Considering the fact that a large part of Dr. Chatard's practice was in the period prior to the discovery of anæsthesia, one must conclude that he was an accomplished and dexterous operator, and the following table gives an idea of his activity in this regard and shows that he terminated every twelfth labor artificially:

Forceps was employed in	372	cases, or	7.8	per cent.
Version " " "	32	" "	0.61	" "
Vectis " " "	4	" "	0.08	" "
Craniotomy " "	26	" "	0.57	" "
Embryotomy " "	1	" "	0.02	" "
	435	cases, or	8.37	per cent.

It thus appears that he applied forceps once in every 14 cases, which was nearly twice as frequently as in the practice of his father, who employed them once in 30 cases and considered that quite excessive, as is shown by the following quotation: "The use of this instrument might have been reduced to three quarters, but feeling certain of not injuring the children and of being able to abridge the sufferings of the mothers, I did not hesitate to make use of it."

It is interesting to inquire how he came to employ forceps so frequently, as at that time it was contrary to the best French and English usage. This is shown by the fact that it was employed once in 78 cases in 55,000 labors reported from the Maternity of Paris between the years 1848 and 1877, and only once in 131 cases in the practice of the Beattys to which I have already referred. On the other hand, it is evident that he did not fall into the error of Osiander, the great apostle of operative interference in obstetrics, who applied forceps in two out of every five cases. This being the case one can only conclude that he evolved the practice from his own experience, as he had found that the operation was harmless in suitable cases, that it spared the patient unnecessary suffering and also did away with the occurrence of certain complications incident to too great prolongation of the second stage of labor.

It is also interesting to note that his neatness came into play in this operation, as he stated that he always washed his forceps in hot water before using them, and applied them while still warm with the idea that he avoided shock to the patient by so doing. Following the French teaching he evidently employed forceps in preference to version, and seems to have limited the use of the latter almost entirely to the treatment of transverse and compound presentations, as his records show

that he performed version in only 32 instances, while he had to deal with 29 transverse and 9 compound presentations.

He resorted to craniotomy in 26 instances, although all but four of the patients were seen in consultation. The fact that he employed an operation which was contrary to the tenets of his church showed that he was not hampered by superstition and used his best judgment in the treatment of his patients. Moreover, the comparatively frequent employment of this operation, as well as the fact that he recorded five cases of death from rupture of the uterus, indicates that even at that time serious disproportion between the size of the head and the pelvis was not unknown, and tends to cast doubt upon the belief that the occurrence of contracted pelves is altogether of recent development.

Dr. Chatard's records concerning the complications of labor present several points of interest. In the first place, he recorded 44 cases of eclampsia with 8 deaths, a mortality of 18 per cent, which is practically as good as that obtained at the present time. No doubt the fact that he practised during a period when venesection was liberally employed contributed greatly to his comparatively excellent results. On the other hand he stated that hæmorrhage occurred in 145 and adherent placenta in 115 cases, a percentage of 2.8 and 2.2, respectively. Such figures are far too high and clearly illustrate the disadvantages under which our predecessors labored, prior to the introduction of modern and more rational methods of conducting the third stage of labor.

He did not believe in the dilating action of the bag of waters, which he believed could be ruptured at any time with impunity. He also held that perineal tears were more often due to the action of the shoulders than to the distension produced by the head; for this reason he strongly urged that the child should not be extracted immediately after the birth of its head, but that its expulsion be left to the unaided efforts of nature.

When I first began the practice of medicine, I frequently heard physicians recommend Chatard's "scattering plaster" in the treatment of engorged or inflamed breasts. Whether this was an invention of the subject of this sketch or of his father, Dr. Peter Chatard, I am unable to say, but in any event it was a widely employed remedy for many years, and Hynson and Westcott tell me that they still keep it in stock, and that even now it is occasionally called for. It consists of galbanum, yellow wax, and olive and linseed oils, and no doubt acts as well as most other remedies; although my own experience leads me to believe that the results obtained were probably purely imaginary, as in such cases the breasts do much better when left absolutely alone than when subjected to treatment of any character whatever.

Possibly the most interesting portion of Dr. Chatard's records is that dealing with puerperal infection, of which he observed 27 cases with 19 deaths, that is one death in every 277 labors or 0.38 per cent. Considering that he practised in the preantiseptic period, such results are excellent and compare more than favorably with the figures of 1 to 212 which LeFort and Husson calculated as the normal incidence in private practice. At the time Dr. Chatard was actively engaged in practice, puerperal fever was the scourge of lying-in institutions, and some idea of its ravages may be gained from the statement that the average mortality in the Maternity of Paris from the years 1802 to 1864 was 5.6 per cent. At certain times it was much higher, and LeFort has stated that it reached 32½ per cent in February and 58 per cent in December, 1864, at a time when something more than 200 women were delivered each month.

Dr. Chatard studied this disease in great detail, and left a separate record giving the history of all his patients who suffered from it, in which it is interesting to note the names of women connected with several of our most prominent old families. He also tabulated the results in the patients treated or delivered immediately before and after the occurrence of this disorder, and, except in the year 1845, discovered nothing which seemed to indicate that the disease might be conveyed from one patient to another. Ordinarily the cases occurred sporadically at intervals of several years, and none were noted after 1871, although two cases occurred in 1844, three in 1848 and two in 1857, but each of them were separated from the others by an interval of at least several months.

In 1845, however, the year made memorable by the appearance of Semmelweiss in the Lying-in-Hospital in Vienna, he had ten cases of puerperal fever. One occurred in February and another in May, but in the period extending from October 7 to December 11, he delivered 25 women, eight of whom developed puerperal fever and six died. Three of these cases were consecutive, while the remainder were interspersed between normal cases. Even this experience, however, did not convince him of its infectious character and shows how difficult it was for our predecessors to comprehend its true nature. After this epidemic he left town for an extended vacation, though I imagine it was more to allay the fears of his patients than to rid himself of any supposed contagion; for at the end of his tabulation he stated "During my long practice of medicine, while attending cases of small-pox or its various modifications, scarlatina, typhoid and typhus fever and puerperal fever, I have taken no particular precaution except to keep my hands clean and washing them frequently, and particularly before attending obstetrical cases. This for the purpose of avoiding innoculation which might otherwise occur, my personal experience leading me to the conslusion that diseases are not carried by the dress or person of a physician."

His son, Dr. F. E. Chatard, utilized this material in an address before the Baltimore Gynecological and Obstetrical Society on the "Communicability of Puerperal Fever," which appeared in the *Maryland Medical Journal,* 1888, XVIII, 467-470, in which he concluded that antiseptic precautions were unnecessary and it is interesting to note that many who took part in the discussion held similar views.

What a contrast to the present time when everyone knows that practically all serious cases of puerperal infection are due to the streptococcus and can be prevented by the employment of strict aseptic technique. It is hardly necessary to refer to

the results now obtained, but the change in hospital results is almost miraculous, and Pinard reports a septic mortality of 0.15 per cent in 45,633 cases delivered in the Baudelocque clinic during the eighteen years ending with 1909, and Mermann of Mannheim one of 0.08 per cent.

With this exception it is apparent that Dr. Chatard's obstetrical work was well in advance of his time and gave results of which anyone might be proud, and I regard it as a great privilege to be able to bring the facts before you.[1]

[1] Dr. J. Albert Chatard has recently presented to the library of the Johns Hopkins Hospital a valuable collection of medical books which belonged to his father and grandfather. Among these are some rare works so that the gift is one of the most important acquisitions that the library has received.—Editor.

ON THE CUTANEOUS DISTRIBUTION OF THE SUPERFICIAL RAMUS OF THE RADIAL NERVE AND ITS COMPENSATORY EXTENSION.

By Irving Hardesty,

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Total absence of function of the branches of two of the three nerves distributed to the lower forearm and hand produced with destruction of the tendons of the forearm, but leaving the hand intact, seems of comparatively rare occurrence. More than a year ago Dr. Harry M. Sherman, of the Department of Surgery of the University of California, submitted to me a patient of his who had suffered an injury of the ulnar side of the forearm, resulting in the destruction of both the ulnar and median nerves, and later he kindly allowed me numerous opportunities to examine the case. The study resulted in a few observations which may be of general interest. These observations include (1) corroboration of the position and extent of the cutaneous area of the hand and wrist supplied by the radial nerve; (2) proof of the retardation of growth and regeneration by scar tissue; (3) retardation of growth of peripheral nerve fibers by impaired nutrition of the tissues to be innervated, and (4) the tendency on the part of the intact nerve toward a compensatory extension of its area into domains not originally occupied by it, but which have lost their usual innervation.

Surgical History of the Case.

Dr. Sherman supplied the following history of the case:

F. L., æt. 50 yrs., a miner.

In August, 1905, he had his left forearm caught between cogwheels and suffered a severe crush with fracture of the ulna and laceration of the flexor tendons on the middle and ulnar side of the forearm. Both the median and the ulnar nerves were severed and implicated in the slough.

Healing left a sound ulnar bone with a scar, depressing the skin surface and attached to the bone, occupying the middle and ulnar regions of the lower half of the forearm.

Patient was unable to use the flexor muscles of the forearm except the radial flexors of the carpus. He had slight control over the thumb. There was no sensation in the fingers except the radial side of the index finger. There was sensation in the thumb. The palm of the hand had sensation external to a line drawn between the first and second metacarpal bones. There was no sensation on the ulnar side of the forearm. On the back of the hand the anesthesia and the sensation corresponded to the ulna and radial nerve distributions respectively.

An attempt was made to unite the median nerve to the radial by reflecting a flap from the side of the median and carrying it over to and inserting it into the radial. In doing this the integrity of the radial was very carefully preserved, for the result of the procedure was so problematic that it seemed unwise to jeopardize the radial conductivity. At the same time the contact was adequately made. An attempt was made to reunite the severed tendons. This was found impracticable because of the union of the scar to the ulna, so the scar was dissected out and a flap of skin was turned up from the chest, the arm brought up to it and the flap sutured to the forearm. When it had united, the flap and the arm were detached from the chest. At a later date and after all wounds in the forearm had healed, a silk tendon was put into the flexor muscles of the forearm and carried underneath the flap and stitched to the cut tendons just below the wrist. It was found impracticable to isolate individual muscles and individual tendons and so a common flexor tendon for all of the fingers was arranged for. This process took a long while and when all of the wounds had healed, the man had recovered flexion of his wrist, but had not individual flexion of the fingers or flexion of the fingers collectively. There was no evidence that any function was permitted by the union between the median and the radial nerves.

When Dr. Sherman submitted the patient to me, more than two years had elapsed since the accident resulting in the injury, and my first examination was made about nine months after the last operation, the grafting on of the skin flap from the chest, had been performed. The wound had completely healed, but the skin and general condition of the hand yet indicated considerable impairment of the blood supply due, in part, to incomplete restoration of the supply destroyed in the wound, and in part to loss of nervous vascular control.

As seen in the history, the original injury, produced by the crushing and tearing of the forearm by the cogwheels, was so serious as to produce far more complicated disturbances than result from simple accidental severing of the ulnar and median nerves. Not only the nerves but the flexor tendons and portions of the muscles of the ulnar side and the median or front side of the forearm were lacerated by the cogs. In addition, there was the considerable sloughing accompanying the first healing and the formation of a large amount of scar tissue which involved the frayed ends of the nerves and tendons, and which made it necessary for Dr. Sherman to remove the scar tissue and graft on a flap of skin from the chest. This necessity resulted in further confusion due to the actual loss of original tissue and to the transplanting of strange skin in the area affected.

Thus, the general symptoms were more extensive than are

described as resulting from section of the nerves alone. The characteristic claw-hand had developed, as was to be expected from loss of the ulnar and median nerves, but, due to destruction of the flexor tendons, the metacarpals and first phalanges of all the digits showed more over-extension than usually described from injury to either or both of the nerves alone, and the second and third phalanges seemed less flexed. There was but a slight ability to control the thumb. Its terminal phalanx could be imperfectly flexed and extended, and the thumb could be slightly adducted, but its metacarpus and first phalanx maintained a general position of extension and abduction. There was a total inability to spread out the remaining digits or to further flex and extend them, and the power of pronation was lost.

Owing to the confusion resulting from the destruction of the tendons and injury to the muscles and the very imperfect muscular activity possible even in the event of complete restoration of the nerve supply to the muscles, all attempts to determine evidences of growth and regeneration of nerve fibers to the muscles were discarded. It was decided to confine attention solely to cutaneous distribution proper. Sensations manifest in the tela subcutanea and fascia appeared too vague and indefinite along the margins of the anesthetic areas to be satisfactorily located and delineated.

The ordinary method for determining the extent of cutaneous sensations was pursued in the following way:

At intervals varying from two weeks to two months the patient was taken into a quiet and warm room, his arm bared to the elbow and extended on a small work-table and upon a cushion of warm towels, and covered with warm towels. Owing to the impaired circulation of the hand and forearm it was deemed of prime importance that, throughout each period of examination, the skin be maintained as uniformly as possible at or slightly above normal blood temperature. Especial care was taken that the patient's position, seated at the table, was as comfortable as possible. The patient was then blindfolded. An esthesiometer of the model devised by Max von Frey was used for all the studies, with the bristle extended 7 mm. Beginning well within the known anesthetic area, the skin was pricked vertically at intervals of 2 to 3 mm. in a line toward the area known to be sensitive. The pressure exerted in pricking the skin was controlled by continuing it in each instance till the bristle just began to bend, and then suddenly removing it. The patient was directed to indicate by the word "yes" his first perception of cutaneous sensation, and the prickings were made about 2 seconds apart to give time for discrimination. Upon the sign "yes" being given, an assistant, who likewise watched the point of the bristle, made a small dot of India ink upon the spot stimulated, using a fine-pointed camel's-hair brush. The lines of prickings, passing from the anesthetic toward esthetic regions, were made from 5 to 10 mm. apart, depending upon the locality. Whenever there was doubt as to the point at which sensation began, a line of prickings was repeated. When the ink dots were made at sufficiently frequent intervals, indicating points in the margin of the sensitive area, the dots were carefully joined into a solid line with the brush point carrying India ink. Thus a continuous black line was obtained defining the boundary between the areas.

The hand and forearm were next photographed in three or four positions. The dorsal and palmar surfaces and the ulnar aspect were always taken, and sometimes both the radial and ulnar aspects. Attempt was made to make all the photographs to scale. Tracings were made from these photographs of the hand and forearm, and the ink line upon them, which latter always came out sharply. Figs. 1 to 5 are reproductions of 12 of these tracings, with the sensitive area filled in with stippling.

The fact is appreciated that determinations of the boundaries of sensitive cutaneous areas are usually untrustworthy as to accuracy, due to the vagueness of the sensations along the border line, and especially to the varying mental equations of both the patient and the operator. Every precaution was taken to guard as much as possible against inaccuracies. The hand and forearm were kept warmed during each examination; the examinations were made under similar conditions of quiet and room temperature. To guard against errors arising from fatigue, the blinder was removed at intervals of about 15 minutes and the patient was induced to turn his attention to other things. During these intervals, the warm towels, upon which the arm and hand had rested and with which they were partly covered, were renewed. Fortunately, the patient was a man of remarkably unexcitable disposition and understood very little of the object of the investigation. His attention was confined to giving the sign as directed, and only upon perception of positive pricking sensations from the skin. Sensations of pressure by the bristle were often mentioned, but disregarded as subcutaneous rather than cutaneous.

Owing to the well-known fact, noted by Tillmans,[1] Thorburn and Williamson,[2] and others, that adjacent territories of nerves overlap each other through the interextension of the collateral and terminal twigs of the nerves, it is realized that the territories of different nerves rarely appear sharply defined. In this case, however, all the nerve twigs for the skin of the hand were totally destroyed except the twigs of the intact superficial ramus of the radial nerve, and thus all sensations manifested on the hand, at least, could be interpreted as mediated through this nerve alone, and the boundary established on the hand could be considered the boundary of the area of this nerve. As indicated below, the nerves supplying the sensitive areas on the wrist and forearm, joining the area of the radial, could be quite approximately determined because their terminal twigs also had been practically isolated in the original destruction of tissue and by the grafting on of the flap of strange skin.

Considering the conditions always to be met in investigations of this kind, the boundary lines obtained in the frequent examinations were remarkably constant and the varia-

[1] Tillmans: Archiv für Klinische Chirurgie, 1882, Bd. 27, p. 1.

[2] Thorburn and Williamson: Encyclopedia Medica, 1901. Vol. 8, p. 282.

Oct. 30, '07.
Fig. 1a.

Nov. 26, '07.
Fig. 2a.

Jan. 26, '08.
Fig. 3a.

Fig. 3c.

March 30, '08.
Fig. 4a.

Oct. 6, '08.
Fig. 5a.

Fig. 1b.

Fig. 2b.

Fig. 3b.

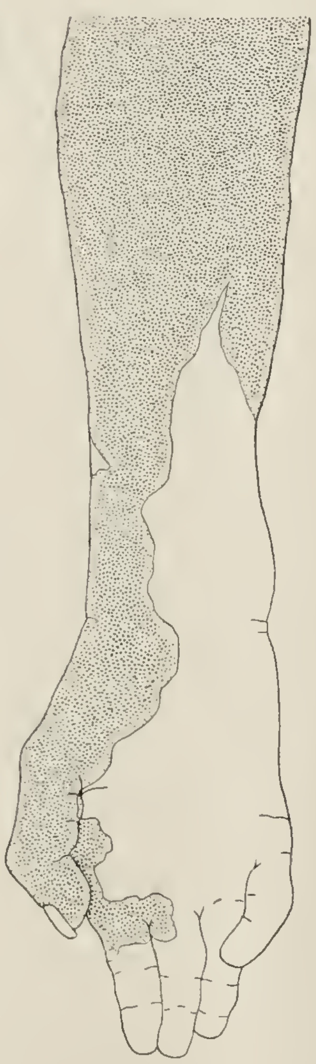


Fig. 4c.

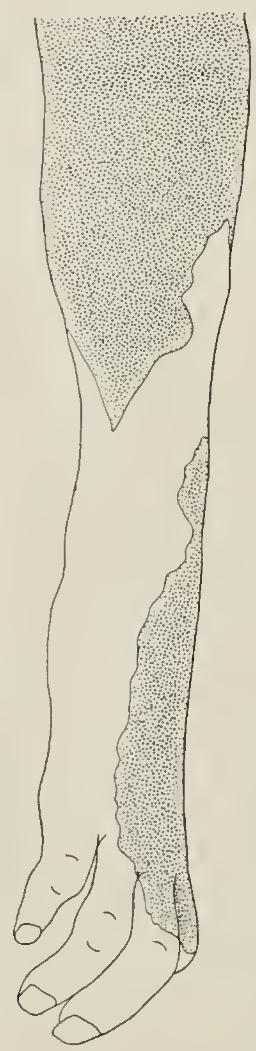


Fig. 4b.

Fig. 5b.

tions manifestly indicating changes in innervation are considered quite trustworthy.

In the tracings of the photographs here given, the boundary lines with the variations due to changes in the innervated area do not appear throughout in their exactly true relative positions, due to the fact that the given positions of the hand, with reference to the camera, were not always exactly identical. The varying amounts of foreshortening, because of the slightly varying positions of the hand, have resulted to greater disadvantage in the tracings than showed in the photographs where the effects of shadow and perspective were present. Attempts were made to photograph in identical positions throughout, and the slight effects due to variations in the angles of exposure were not realized till the tracings were made and compared, which was after all the photographs had been taken. These effects, however, do not seriously obscure the few points of interest. The effect is most marked in comparing Fig. 2a with Fig. 3a. In Fig. 3a the ulnar side of the hand was turned outward, toward the camera, more than in Fig. 2a, in which the dorsum was squarely exposed.

Fig. 6.

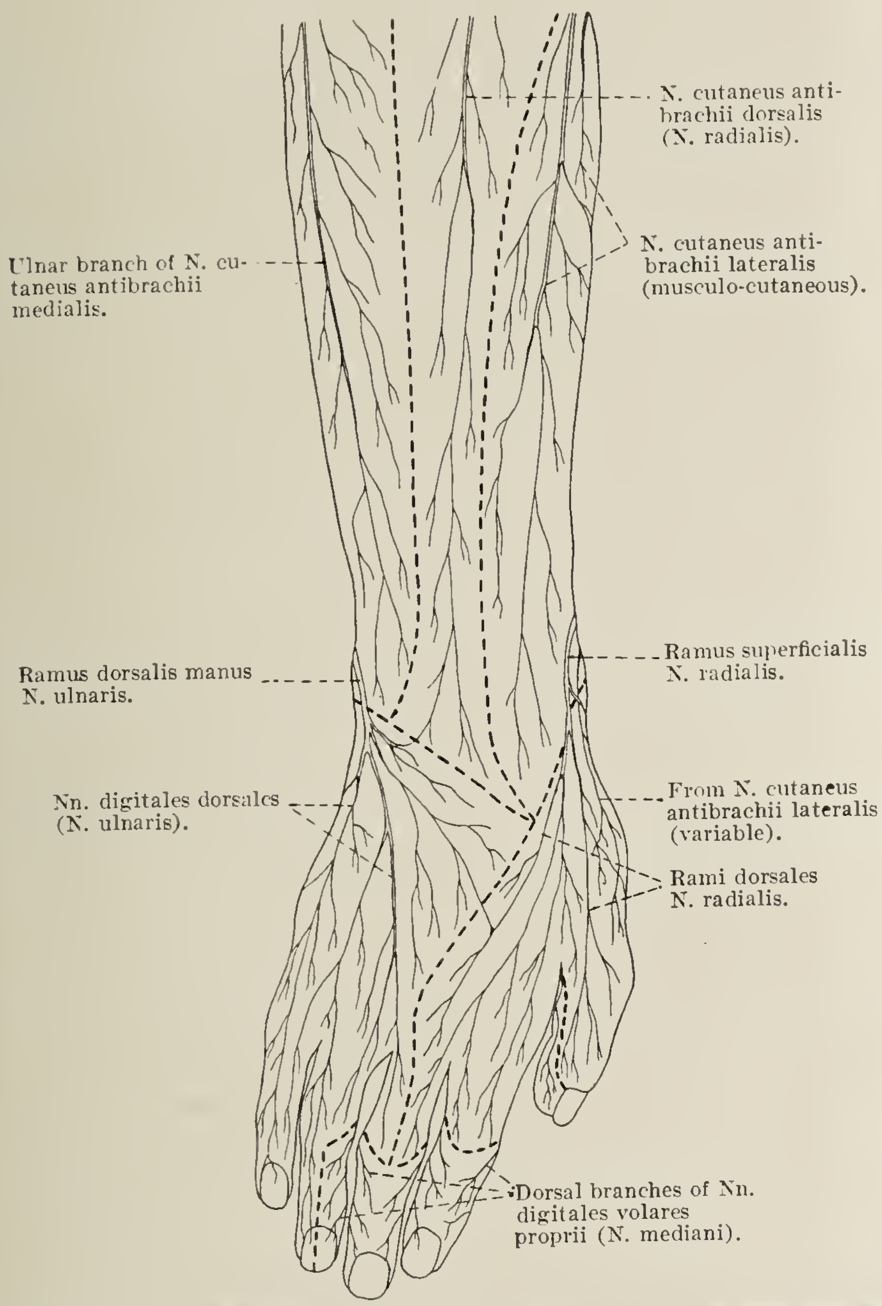
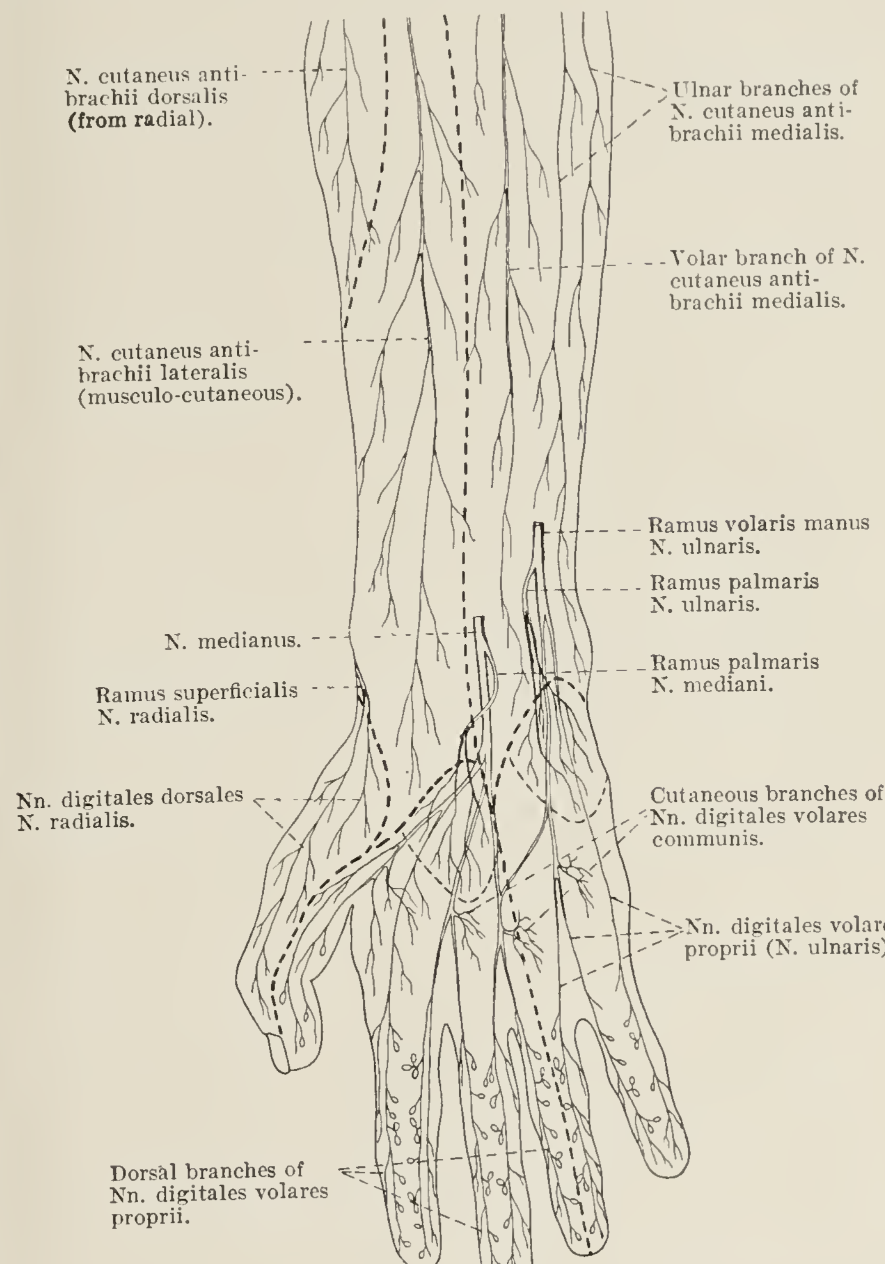


Fig. 7.



The common or average areas of cutaneous distribution upon the hand and wrist of the ulnar, median and radial nerves are sufficiently familiar to all, so their description here is unnecessary. The usual territory supplied by each has been repeatedly determined by dissection, experimental stimulation after section, and by study after degeneration following accidental division or destruction of the nerves. The literature of the past 50 years abounds with descriptions of cases, most of them detached and more or less crude, but which, taken together, have rendered it possible to outline the normal or usual areas of distribution of each of the nerves. Likewise there are abundant papers and notes describing instances of abnormal distribution of these nerves. Kennedy [3] was the first to give a complete and systematic summary of the literature upon the regeneration of sectioned nerves, and to draw general conclusions as to areas of distribution upon the limbs based upon information assembled from numerous cases. Including that collected by Cruikshank, he gives a bibliography extending backward as far as 1537. Sherren,[4] in two lectures, sums up previous findings and opinions as to the areas supplied by the nerves to the limbs, combined with

[3] Kennedy, R.: Phil. Trans. Royal Soc., Vol. 188, 1897, p. 257.

[4] Sherren, J.: Lancet, 1906, Vol. I, p. 727.

results obtained by himself from personal study of 175 cases of nerve injury. Tonkoff[5] gives one of the collections of descriptions of abnormal arrangements of the cutaneous nerves to the back of the hand, comparing and explaining them on the basis of the normal arrangement of the same nerves in the apes.

For ready reference in connection with the case here in hand, Figs. 6 and 7 are given. These are compiled from various findings and similar diagrams in text-books of anatomy, and are considered as showing the average or usual cutaneous areas of the forearm and hand supplied by the respective nerves as indicated.

Several cases are recorded in which the ulnar and median nerves were severed. These may be divided into those in which the nerves were clean cut (glass cuts, knife wounds and all strictly localized injuries), and those in which the nerves were lacerated, accompanied by the destruction of considerable other tissue, as in the case here described. Sherren (loc. cit.) makes a distinction between subcutaneous sensations, "deep sensibility" or "deep touch," and direct cutaneous sensibility, "light touch," and states that "deep sensibility" is not present when the tendons of the extremity are destroyed or even severed. He bases this conclusion upon the study of cases in which the cutaneous nerve branches are destroyed both with and without accompanying destruction of the tendons beneath. This probably means only a serious impairment of the subcutaneous sensations due to the severing of the nerves and the degeneration of the plexuses which accompany the tendons, many of whose fibers terminate upon the tendon sheaths and bones and in the muscles. In addition, a few of the sensory fibers ending in the subcutaneous connective tissue may not be severed with the division of the tendons, and there should remain, with severed tendons, a certain amount of deep sensibility dependent upon the cutaneous nerves proper.

In the case here in hand, a considerable extent of the flexor tendons had been totally destroyed, but there was occasionally noted along the inner margins of the anesthetic area indications of deep sensibility under skin having no direct cutaneous sensibility. These were more frequently remarked during the latter part of the study, when regeneration of the cutaneous nerves had become a little more rapid. They are mentioned as indicating that the growing nerve twigs extend in the loose subcutaneous tissue in advance of the region in which they are actually terminating in the skin proper.

In the absence of the cutaneous supply to the hand from the ulnar and median nerves, the distribution of the radial (the only sensitive area remaining upon the hand) appeared to conform quite closely to the average or normal distribution of this nerve. On the dorsum of the hand, the area extended slightly upon the ulnar side of the first phalanx of the middle finger (Fig. 1a) instead of to the mid-line of this phalanx, and thence curved toward the ulnar side of the dorsum rather than toward the radial side, as does the average or normal area (Fig. 6). However, judging from the subsequent studies, this apparent abnormality of the area is considered as probably due in part to the compensatory extension of twigs from the radial already begun during the time between the injury and the time the first study (Fig. 1) was made, and partly, from above, to the terminal twigs of the lateral cutaneous antibrachial nerve.

On the palmar aspect, the boundary line of the sensitive area was normal for the radial supply to the thumb, extending toward the volar surface to a line beginning at the lateral margins of the nail and passing thence parallel to its first and second phalanges (Fig. 1b). Thence, instead of curving radialward to terminate the area just above the radial edge of the wrist joint (Fig. 7), the boundary line turned medianward to include the greater part of the thenar eminence, and then upward upon the forearm to the line of suture of the skin flap grafted upon the forearm. This course is due to the fact that the cutaneous area of the radial nerve is joined on the thenar eminence by the area supplied by the lower end of the volar branch of the lateral cutaneous antibrachial (musculo-cutaneous) nerve, a part of which area here comprised the only isthmus of sensitive skin connecting the unaltered skin of the forearm, above the grafted area, with the hand (Fig. 3c).

The flap of the skin from the chest, grafted onto the forearm after removing the large amount of cicatricial tissue resulting from the original wound, was finally detached from the chest wall on January 28, 1907, and the final stitching into the forearm made. Thus it was during the month of February, 1907, that the usual sloughing and healing processes were completed, and it was not until the latter part of the October following that the patient was first subjected to the study described here.

Notwithstanding this length of intervening period, the first study with the esthesiometer revealed practically no invasion of cutaneous nerve fibers into the grafted area. Almost throughout its entire boundary the line of suture of the graft, which could be distinguished as a line of scar in the skin, was likewise the line of demarkation here between the sensitive and anesthetic surfaces. Much of the grafted area itself still had the characteristic smooth, glistening appearance, but with a color showing a better vascular supply than had the suture line.

Beginning with the bristle within the grafted area and working toward the suture line, no sensation was manifest during the first study till the suture line was crossed. Then, suddenly, on the immediate sensitive side of the suture line, not only sensation was manifest but hyperesthesia and often of considerable amount. The patient would suddenly cringe, uttering a loud "yes." This is considered as indicating that the cutaneous nerve twigs, severed by the injury and operation, spreading in the corium toward the grafted area, and terminating in the stratum papillare and epidermis, had been resisted by the density of the scar tissue along the suture line. The obstruction had caused the growing ends to be reflected

[5] Tonkoff, W.: Internat. Monatschrift für Physiol., Bd. 15, 1898, p. 156.

and become coiled up along the sensitive side of the scar line, giving the skin immediate to the line an especially abundant innervation. In Figs. 1a and 1b the boundary shown of the anesthetic area of the forearm is coincident practically throughout with the line of suture of the grafted area.

In subsequent studies, when the tests showed that in places the growing nerve fibers were succeeding in breaking through the line of sutural scar tissue (Figs. 2a and 2b), the boundary of the anesthetic area became more and more irregular. And it is interesting to note that wherever along the line sensation invaded the anesthetic area by passing through the scar line, the line of hyperesthesia disappeared. Painfully sensitive before breaking through the scar, the line became normally sensitive afterward.

The obstructive effect of scar tissue against the extension of regenerating and growing nerve fibers is of common experience, especially as formed in the region of division of nerve trunks. Among others noting the effect, Holmes [6] reports a case of operation six months after the radial nerve had been severed, in which the end of the central stump was found involved in a dense knob of connective tissue. This knob had totally obstructed growth extension, and in it the regenerating fibers were coiled and gnarled, increasing its density.

One might expect that the anesthetic area of the forearm, represented by the area of the grafted skin-flap, would acquire its innervation, beginning along its upper border and gradually spreading from this border downward toward the hand. This would seem the natural direction of procedure from the fact the severed nerves which normally supply the lower part of the forearm are the terminal and downward-extending ends of the ulnar and volar branches of the medial cutaneous antibrachial nerve (internal cutaneous nerve), the lower cutaneous arm branch of the radial or musculospiral (N. cutaneus antibrachii dorsalis), and the terminal portions of the volar and posterior branches of the lateral cutaneous antibrachial nerve (cutaneous portion of the musculo-cutaneous nerve). The arrangement of these is indicated in Figs. 6 and 7. A wholly downward spread of the regaining innervation, however, was by no means the case. The spread of cutaneous sensibility from the original boundary into the anesthetic area was about as rapid from the sides and even from below as it was from above. The spread from below, because of the locality of the injury and the position of the grafted flap, was of necessity from the radial side, and is explained as due to the growth of lateral twigs from a probably uninjured terminal cutaneous branch of the musculo-cutaneous nerve and, further, to the growth of lateral twigs from the superficial branch of the radial (radial nerve of the older nomenclature). From the general downward normal direction of the twigs of the superficial branch of the radial, such lateral twigs from it into an area not previously supplied by it would indicate a tendency toward compensatory innervation on the part of the radial.

Compensatory extension of the area of the hand normally, and here originally, supplied by the radial was quite positively indicated. The first examination of the patient showed that the area of the hand supplied by the superficial branch of the radial corresponded quite closely to that usually given as the normal area of the radial (Figs. 1a and 1b). Though nine months had elapsed since the grafting of the skin and about two years since the original injury, so great had been the impairment of nutritive functions by the laceration and growth of scar tissue that at the first examination but little evidence was manifest of innervation advancing into the area rendered anesthetic. On the dorsum of the hand and wrist (Fig. 1a), the sensitive area extended further toward the ulnar side than does the usual area supplied by the dorsal branches of the radial (Fig. 6). This is explained above as due in part to the downward extension of the terminal twigs of the lateral antibrachial cutaneous (musculo-cutaneous) nerve, which was probably uninjured by the accident and operation, and in part either to a larger dorsal area than usual supplied by the radial, or to an already begun compensatory extension of twigs from the dorsal branches of the superficial branch of the radial to the skin of the wrist and dorsum of the hand. It has been noted that the skin of the dorsum of the hand is not always supplied by the ulnar and superficial branch of the radial alone. Zander [7] called attention to the fact that twigs from the lateral cutaneous antibrachial (musculo-cutaneous) and the dorsal cutaneous antibrachial nerve (external cutaneous branch of the radial) may take part. The latter branch was involved in the injury and its area involved in the skin graft, so that it was not represented at all in the dorsum of the hand. The former nerve, however, was no doubt represented, and very probably took part in the upper part of the extension of the sensitive area.

The cutaneous supply over the dorsal surface of the first phalanx of the third or middle finger and the adjoining end of the third metacarpal was practically that usually given for the radial nerve, i. e., sensation was present over only the radial half of the first phalanx and the line curved slightly ulnarwards over the third metacarpal.

The radial supply to the skin of the thumb, at the time of this first examination, was likewise that usually described. Normal sensation was present over the dorsal or outer surface of the thumb, but only over the root of the nail (the skin forming the vallum unguis). Along the lateral aspects of the thumb the sensitive area was sharply bounded by lines continuous with the lateral margins of the nail. On the mesial side this line curved slightly from the margin of the nail toward the volar surface and then became straight along the side of the thumb. The line on the lateral side was quite straight on the extended thumb, parallel to and continuous with the lateral margin of the nail, till, reaching the palmar surface covering the first metacarpal, it curved mesially to include the greater part of the thenar eminence. Thence it did not follow the margin of the usual radial area by curving lat-

[6] Holmes, T.: Lancet, 1883, Vol. I, p. 1034.

[7] Zander: Berliner klinische Wochenschrift, 1890, No. 8.

erally to the radial margin of the wrist. This was obviously because of the fact that the sensitive area of the radial was joined on the thenar eminence with the area supplied by the terminal of the volar branch of the lateral cutaneous antibrachial nerve (Fig. 7).

From Fig. 1 to Fig. 5, a and b, the tendency toward compensatory extension manifested by the radial nerve during the months under observation may be seen. A study made between those represented by Figs. 1 and 2 showed a beginning extension of the area of the radial on both the mesial and lateral sides of the thumb and toward the volar surface of the index finger. However, the portion of the sensitive area first to reach the actual palmar surface extended from the dorsal aspect in between the index and middle fingers instead of passing around the lateral aspect of the first phalanx of the index finger. In Fig. 2b this had fused with the extension around the index finger and second metacarpal. Two months later (Fig. 3b) the entire thumb was normally sensitive, and the new palmar area had extended slightly. Thence the compensatory extension continued, though remarkably slowly, both on the palmar surface of the hand and outward on the dorsal aspect of the three fingers and hand, as shown in the figures. The remarkably slow extension was probably due to two causes: (1) the impaired vascular supply to the hand and, therefore, the impaired nutrition, and (2) to the fact that the extending nerve fibers had to penetrate absolutely new and, to them, strange territory, being neither nourished nor guided along paths of least resistance by the terminal stumps of degenerating fibers. Further, it is probable that the fibers so extending were not only slow but were few at the time. Ingbert[8] has computed that in the cutaneous innervation of man, one fiber in an arm nerve supplies an average of 1.3 sq. mm. of skin. Thus comparatively few fibers may have been taking part in the compensatory extension.

[8] Ingbert, Charles: Jour. Comp. Neurology and Psychology, Vol. 13, 1903, p. 209.

As mentioned in the history of the case, Dr. Sherman made an attempt to unite the stump of the median nerve to the trunk of the radial, but taking especial care not to injure the radial. There is a remote possibility that the extension of the hand area of the radial may have been accomplished by fibers grown onto the radial from the median nerve. This is very improbable, however, for the median nerve could have been, with safety, scarcely more than inserted into the sheath or epineurium of the radial, and the density of this sheath would offer greater obstruction to the fragile regenerating ends of the median nerve fibers than would the much looser areolar fascia about it. Further, the distance these fibers would have to extend, compared with the rate at which regeneration was taking place in the other localities of the forearm, and the probable total absence of the guiding influence of degeneration in the radial render very doubtful the presence of median nerve fibers in the terminal twigs of the superficial branch of the radial.

After having the patient under observation for about a year, he was allowed to go unmolested further and, expressing an intention to return to the mining region whence he came, he was lost sight of.

DESCRIPTION OF FIGURES.

Figs. 1a to 5b.—Tracings made from a series of photographs taken of the injured forearm and hand at the intervals indicated during one year. The boundary between sensitive and non-sensitive areas was in each case indicated on the hand, and in the photographs, by a line of ink, not shown in the tracings. Instead, the sensitive areas are stippled to the position of the line, leaving the non-sensitive areas blank. In each figure, a and b are respectively the dorsal and volar surfaces as photographed after the same study. Fig. 3c shows the radial aspect at the same period as Figs. 3a and 3b, and Fig. 4c shows the ulnar aspect at the same period as Figs. 4a and 4b.

Figs. 6 and 7.—Diagrams considered as showing the more common cutaneous areas of the dorsal and volar surfaces of the forearm and hand supplied by the nerves indicated. The overlapping of the areas is intentionally omitted.

PRIMARY UNION AFTER MASTOIDECTOMY.[1]

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One may well be excused for a feeling of diffidence in appearing before such an august assemblage as this International Congress of Otologists to call attention to a mere detail in the performance of a thoroughly well-established surgical procedure. The modern operation of mastoidectomy, for the cure of acute purulent disease of the cellular mastoid portion of the temporal bone, has been developed to such a state of perfection and, as generally performed by well-trained operators, is giving such satisfactory results that it would seem well-nigh impossible to improve upon it. A glance at the history of the development of this operation, however, shows that its steady growth has been a matter of slow progression and that the present degree of excellence has been attained only through the accumulation of many minor improvements suggested from time to time. It may not be too much to hope then that a still nearer approach to perfection may yet be accomplished and it is with the desire to contribute, if only in a small way, to the further development and perfection of this operation that I dare submit for your consideration this contribution to the subject.

[1] Read at the Eighth International Congress of Otology, held at Budapest, September 2, 1909.

A perfect mastoidectomy, or the ideal operation for the cure of mastoiditis, would seem to comprehend complete eradication of the infection and healing of the operation wound in the shortest possible time; secondarily, it goes without saying, these results should be obtained with the least risk to the life of the patient, with the least discomfort to him while under treatment and with due regard to leaving the smallest possible deformity. The first, and perhaps the most important, part of the operation has been well provided for and to that we need devote no further attention in this paper; in every operation for mastoiditis the surgeon now endeavors to remove every particle of pus, detritus and necrotic or carious bone, even though he be compelled to obliterate the cellular structure of the mastoid tip, the zygomatic process and the occipital region, or to invade the cranial cavity itself. Assuming that this has been accomplished, does it constitute a complete operation?

It is rather to the second portion of the statement regarding idealism that I would respectfully direct your attention—namely to the healing of the operation wound in the briefest possible time. With the majority of operators at the present time it is the custom to treat the mastoidectomy wound as a pus cavity that should be compelled to fill up by granulation from the bottom; the process commonly known as secondary healing. To this end the wound is dressed with sterile or antiseptic gauze at the close of the operations and the dressings are changed repeatedly, at intervals of one to three days, until complete closure takes place—a period of time varying from three weeks to as many months. Removal and replacement of these dressings is often decidedly painful to the patient, always time-consuming and more or less annoying for the surgeon, the period of convalescence is generally a protracted one and the remaining scar is not infrequently a source of much concern to the patient. That these are serious defects in the operation as at present generally performed cannot be denied and, quite as certainly, any improvement looking to the procurement of immediate healing of the wound cavity would confer a benefit upon patient and operator alike. Abolition of after dressings, shortening of the period of convalescence and limitation of the scar or of deformity are certainly desirable improvements and there would seem to be no way to attain these save through the immediate healing of the wound.

For the sake of emphasis, we may repeat the special advantages attending or following primary union of the mastoid wound. In the first place, primary union means that the patient is enabled to leave the hospital at the end of one week; healing of the wound edges is usually fairly firm by the fifth day. This is to be compared with the average period of one month required for healing under granulation by the open method. Secondly, the only after dressing consists in an application of a protective pad or a light collodion dressing for a few days to prevent accidental injury; this instead of the repeated cleansing and packing which an open granulating wound requires and which is always uncomfortable for the patient and troublesome to the surgeon or his assistants. Thirdly, primary union means almost no scar; merely a white line, which three months from the date of operation can be seen only when searched for, as against a broader, thicker band of scar tissue with more or less depression, near its center, according to the rapidity with which the new tissue has been formed.

Admitting the desirability of primary union after mastoidectomy, there are several important questions to be considered, bearing upon the method of procedure and the possibilities of success, that might be discussed, seriatim, under the following headings:

1. A brief history of the efforts made in this direction.
2. Criticisms of such attempts, based upon the fear of additional risk to the patient.
3. Scientific investigation in support of the belief that healing under blood-clot is safe and promising.
4. The clinical evidence as to the possibility and probability of success.
5. The technic which gives the greatest assurance of securing primary healing of the mastoid wound.

1. Historical Sketch of the "Blood-Clot" Dressing.

In 1886 M. Schede published a most remarkable report on his experiences with the healing of wounds under the moist blood scab, his paper appearing in the Verhandlungen der Deutschen Gesellschaft fuer Chirurgie, under the title, "Ueber die Heilung von Wunden unter den feuchten Blutschorf." The timeliness of this contribution and its value in general surgery has been well described in a paper by Professor Halsted, who says, "It was my practice for several years to attempt with the utmost care to obliterate the dead spaces in wounds. The results were gratifying, but the technic was often very tedious. For example, after an amputation of the thigh it would not infrequently take an hour to obliterate all the dead space. The mechanical problems were sometimes quite difficult, and one was perpetually annoyed by the fear that he might strangulate the tissues included in the sutures. After a time I became convinced that it was impossible to obliterate thoroughly all the dead spaces in some wounds, and I observed that wounds in which the dead spaces were not obliterated healed throughout by first intention just as regularly as did the other wounds. I was, therefore, quite prepared to welcome Schede's article on the healing of wounds under the moist blood scab. This contribution by Schede I believe to be the greatest which has been made to the technic of surgery since the introduction of antiseptic methods by Lister."

Now, Schede's work proved not only that there was no danger in leaving blood to clot in clean wound cavities but that in obliterating dead spaces the clot favored rapid healing. It was really nature's plan of avoiding or preventing dead spaces, the then bugaboo of the surgeon, and Schede had recognized the fact. In accordance with his own observations and accepting Schede's suggestions, Halsted applied this method extensively and in 1891 presented his report on "The Treatment of Wounds, with Especial Reference to the Value of Blood-clot in the Management of Dead Space" (Johns Hopkins Hospital Reports, 1891, Vol. III, No. 5, pp. 255-261).

Perhaps the most interesting part of that report, to otologists, is the employment of the method in the treatment of osteomyelitis, since he was there dealing with cavities in bone tissues. The most excellent results obtained by Halsted and his associates in the surgical treatment of this affection were remarkable. He found that the protracted after-treatment of these surgical cases could be avoided and primary healing secured in very many instances; the requisite to success apparently being a thorough removal of the diseased bone and all infective material, with disinfection of the wound cavity before allowing it to fill with blood and closing up.

At about the same time that Professor Halsted was conducting his experiments in the application of the blood-clot dressing to the healing of the wounds in long bones, our esteemed fellow worker in otology, Dr. C. J. Blake, of Boston, was adapting it to mastoid surgery. His first public reference to this work appears in the Transactions of the American Otological Society for 1891, p. 27, where, in reporting the histories of twenty-three mastoidectomies performed during the first eight months of that year, he says, speaking of the treatment of the wound after all diseased tissues had been removed, "The ear itself was carefully dried, plugged with a pledget of cotton or baked gauze, and baked gauze dressings applied over the mastoid region and the ear, in some few cases corrosive being used instead of the baked gauze; *in no case were drainage tubes or gauze introduced into the wound*, and no stitches were used. Twenty-four hours after the operation, unless previously required, the wound was re-opened and explored by means of a probe and syringed with weak corrosive or, preferably, weak permanganate solution, subsequent drainage being insured sufficiently in all cases by the daily probing, the wound being allowed to close from within and above as rapidly as possible, care being taken to preserve, however, by use of the probe at the daily dressing, a sufficient external opening to permit of free drainage and to allow the use of the curette should any smaller spicule of bone, detached subsequently to the operation and detected by the probing, require removal. With the cases thoroughly curetted this was rarely necessary.

"The best results as to time of recovery, including complete healing of the wound to the surface, were, of the twenty-three cases, one in six, one in seven, one in nine, one in eleven, and three in thirteen days after the operation."

It will thus be seen that in the first cases treated Dr. Blake was in the habit of probing the wound occasionally during the healing process, partially breaking up the clot, with the object of finding and releasing any possibly retained septic material or foreign body left through incomplete surgical work. Even with this amount of interference the period of recovery was much less than that attending wounds that had been packed with sterile gauze. In the following year Dr. Blake concluded, evidently having gained more confidence in the powers of blood-clot, to omit the probing of the wound at the dressings subsequent to the operation for, in a paper read before the same society (Tr. Am. Otol. Soc., 1892, p. 204), reporting a further series of mastoid operations, he says: "Of the three following cases in which the mastoid cavity was quite cleared of its cellular structure, one was subsequently dealt with by frequent probing, antiseptic syringing and dressing; in the other two cases the excavated mastoid cavity was allowed to fill in with blood-clot at the conclusion of the operation, then superficially irrigated with very hot water—so hot as just not to scald the skin. The edges of the cut were brought together, covered with a cheese-cloth pad, baked dressing and a bandage.

The first case healed in four weeks with a deeply depressed cicatrix.

Of the other two, one was practically healed in five days; the other, the first dressing was made on the third day, and on the fifth day a cotton collodion dressing only was required; and in both, the pain and fever incident to the mastoid disease were entirely relieved by the operation. The greater part of the wound healed practically by first intention, and the cicatrix was insignificant."

Comparison of the results in these cases is very striking. As with so many other discoveries, the first incentive to this investigation came accidentally. A case of acute suppurative mastoiditis which had been submitted to operation and dressed under blood-clot developed an erysipelas of the scalp and face which prevented re-opening of the wound as was then customary. The erysipelatous inflammation ran its course in about ten days and when the dressings were removed from the mastoid the wound was found to be completely healed. The suggestions growing out of this experience led to the comparison in the small group of cases reported above and, later, to its trial in many more.

The next progressive step is related in another paper to the American Otological Society in 1898 (Tr. Am. Otol. Soc., 1898, p. 32), wherein Dr. Blake says: "With the accruing evidence of the possibility of safely avoiding the process of packing and dressing mastoid wounds after mastoid evacuation, came the question of differentiation in the determination of the class of cases to which this method was applicable, and the later series of observations has been made to include the application of the blood-clot dressing to all mastoid operations in the series, including even those of chronic suppurative middle ear and mastoid disease, and excepting only those cases in which the extent of the operative field made it necessary to resort to packing for other reasons.

"The admissibility of this line of investigation in the chronic suppurative cases, where the procedure was not expected to be a success so far as primal healing was concerned, was justified by the fact that the unsutured wound, if giving evidence at its first dressing, forty-eight hours after operation, or earlier, of infection of the blood-clot could be immediately opened painlessly by means of a blunt probe and the wound treated in accordance with its septic condition by cleansing and packing, and this without detriment to the patient by deferring this procedure to the time of the first dressing instead of packing at the time of operation.

"Thus in twenty-five cases of mastoid evacuation made the subject of the blood-clot experiment in 1896-7, sixteen were so-called acute cases, and nine cases of long continued suppuration with later mastoid implication. Of the sixteen acute cases,

seven recovered by primary healing and were discharged well, one in twelve days, two in eleven days, two in ten days, and two in eight days, thus giving an average of ten days. In the nine remaining acute cases and the nine chronic cases it was necessary to reopen the wound in the manner mentioned and allow it to heal by granulations from the bottom.

"In this series of twenty-five cases, therefore, the percentage of recovery in the time mentioned in acute cases is 43 per cent and in the total number of cases in this series 28 per cent."

At about this same time a somewhat similar series of operations were being performed and an analogous method developed by Professor Küster, of Marburg. His operation has never been widely adopted but its success was in the main dependent upon the same principle involved in Dr. Blake's work—the value of rapid healing under blood-clot. In the Journal of the American Medical Association for November 2, 1907, p. 1505, Küster says: "Under the title 'Ueber die Grundsaetze der Behandlung von Eiterungen in starrwandigen Hoehlen' (On the principles of treatment of suppuration in stiff-walled cavities) I published in 1889 an essay in which I recommended a broad opening of suppurating sinuses in the pleura, the cavities of the forehead, upper jaw and mastoid process, and proved the efficacy of the method in many cases. At first I made simple incisions to the bone, which I later changed in accordance with the principles of osteoplastic surgery to avoid deformities.

"I am very glad to find that the principles of operation which I then stated have been the basis of the development of this part of otiatric science. Still it must be acknowledged that a great many improvements in technic and instruments have been added to the primary method. However, after demonstrating that the opening of the mastoid by a straight-lined incision often produces an ugly deformity in the shape of a deep cavity behind the ear, I began in 1895 to form an oblong flap with upper base out of the whole skin, periosteum and a thin layer of bone of the mastoid process. This flap is folded back, the antrum, and in grave suppurations also the tympanic cavity, is opened with a chisel and after cleaning the field of operation the flap is reimplanted. The cavity under the flap is filled up by granulations and heals in a few weeks. I performed many of these operations and had cosmetically good results. My publication was violently attacked by several aural surgeons. They said that the reimplantation flap must hinder the survey of the wound and that it must be impossible to observe the condition of the disease. I replied that the latter may be judged better without looking into the open wound, as this would not be without danger for the life of a bone. A continuous suppuration indicates the persistence of the disease and requires the re-examination of the wound by lifting the flap. In the majority of cases I saw a prompt and persistent healing in a few weeks. Further, my adversaries said that the straight-lined incision gives the same cosmetic results; meanwhile I, and other surgeons, have been obliged to cover by plastic operations very ugly holes behind the ear made by aural specialists. Such a result is prevented by forming a flap even without bone; but the normal vault is only to be obtained by osteoplastic operation."

It may be observed in passing that Küster's criticism of the usual mastoid operation, where healing by granulation is awaited, is perfectly fair and that the claims of advantage in this method are well founded. The operation is rather more difficult to perform than the one described by Blake and possesses no advantage over the latter; the deformities and persistent fistulæ that Küster complains of are not due to the straight-lined incision, but to the slow and imperfect process of healing; if the straight-lined incision be followed by a complete operation and the wound closed for primary healing under blood-clot, the results will be even better than those obtained by Küster.

Following the lead of Dr. Blake a steadily increasing number of operators have adopted the plan outlined in his report, until to-day the method is employed more or less frequently by many American otologists. The application of the method has been subjected to various modifications but no one has effected any materially beneficial alteration. Thus, some speak of a "modified blood-clot" operation, meaning that a small drain of some sort is inserted between the edges of the wound and left until the second dressing to prevent any possible tension on the sutured wound, by draining away any serum exuding from the clot; their results are fine and show a marked improvement over the old plan of providing drainage, but, inasmuch as equally satisfactory results are gained without this drain it would seem to serve no useful purpose. The most practical improvements suggested have been those bearing upon the cleansing of the wound, it having been shown by the author (J. Am. Med. Ass., March 31, 1906) that excessive efforts at chemical sterilization of the bone cavity tends to interfere with organization of the blood-clot, and, the subcutaneous suturing of the wound margins to effect better coaptation and consequently a reduction of the scar to a mere line.

2. Objections Raised Against the Method.

It was perfectly natural and proper that other surgeons should criticise this innovation upon an established form of procedure. It is a good rule to test all things and hold fast to that which is good. In surgery, particularly, must we be slow to accept unproven modifications. The patient's interest must be considered above any possible gain in time or labor to the physician and every precaution taken to safeguard the welfare of the patient. Therefore, it was not strange that men should hesitate to fill a bone cavity, made by the removal of infective material, with the patient's own blood and close, or even suture, the skin over that blood-filled wound. Fear of the possible consequences of enclosing in the wound some microscopic particles of infective material and, secondly, a belief that the normal blood-clot constituted a favorable medium for the growth of bacteria naturally accounted for a disinclination on the part of many to even try the method. I can conceive of no other important objections, and, so far as I am aware, these are the only ones that have been urged against it. No one has ever reported a fatal result attributable to the blood-clot dressing in surgery and the only risks spoken of are based upon theoretical reasoning or, rather, upon a vague fear of something happening.

3. Reasons for Considering Healthy Blood-clot a Safe Dressing for Wounds.

Let us consider these objections from a scientific point of view and ascertain in how far physiological experiments explain what happens when a clean cavity in bone is filled with healthy blood-clot and what power such a clot may have to overcome infective material that may have been inadvertently left in the wound. Experimental and clinical studies have shown that if *any* clean wound be filled with the patient's own blood, and safeguarded from later infection, the blood-clot tends to organize and new tissue, similar to that enclosing the clot, soon forms to replace the latter. The blood flowing into the wound cavity rapidly clots and the fibrinous frame work of this clot constitutes a scaffolding on which the new tissue is built. Fresh granulations spring from the walls of the cavity and grow out into the clot, forming a new fibrous connective tissue, the nature of which is further altered to accord in character to the surrounding cavity walls; that is, if the wound be made in bone, osteoblasts are sent out from the bony walls or from the periosteum to convert the fibrous substance into osseous tissue. The migratory power of these osteoblasts is limited and they travel only a short way from their starting point so that, in the case of a large cavity in bone, the newly formed bone does not extend far from the cavity wall and the center of the new-formed tissue remains fibrous in character. It seems quite probable, however, that in a small cavity, such as we ordinarily have in the mastoid process, the osteoblasts reaching out from all directions, may extend a sufficient distance to meet in the center and thus to complete the construction of a new bony process. Just how early this osteoblastic activity commences is not known, but such cells have been observed to form within forty-eight hours after the operation and it is certain that granulation tissue grows more rapidly into a healthy blood-clot than into space. It is plain, then, that nature may be greatly aided in the reconstruction of destroyed tissue by providing an excellent frame-work on which to build and leaving her only the task of furnishing vascularity and new tissue cells.

Some very interesting observations upon the regeneration of bone have been made in recent years, through animal experimentations, by Dr. E. H. Nichols, of Boston (J. Am. Med. Ass., 1904, Vol. XLII, p. 439), and Dr. H. S. Vieder, of Philadelphia (Univ. of Penn. Med. Bull., 1908 Vol. XX, p. 109). After explaining the process of regeneration Nichols states that the power of repair of dense cortical bone is very slight or practically wanting and that removal of sequestra leaves a more or less extensive cavity in the bone, surrounded by a wall of dense bone lined with unhealthy granulations, which has no tendency to close. He further observes that the most satisfactory methods ordinarily recommended for the closure of such defects are the aseptic blood-clot, or obliteration of the cavity and approximation of skin flaps. Wieder's experiments concerned themselves more particularly with the exact process of regeneration and in ascertaining the source of osteogenesis. He proves pretty conclusively that in the regeneration of bone all of the various elements, viz., periosteum, cortex, endosteum and marrow, participate in the process, but that the periosteum plays a minor part as compared with the amount of new bone furnished directly from the surrounding bony walls. This is exactly in accordance with the views expressed by MacEwen many years ago (Annals of Surgery, 1887, Vol. VI, p. 289) and would seem, furthermore, to point to a possible additional advantage in the Küster operation, which leaves the largest possible area of bone surface capable of furnishing osteoblasts.

The second point that we wish to consider has to do with the properties of the blood, the dressing which we are introducing into the wound cavity. Let us suppose that this cavity has not been made absolutely clean, that some invisible particle of septic material is present when the blood is introduced, has the blood any bactericidal or antitoxic powers? A long series of observations by the most careful investigators has clearly proved that the normal human blood *does* possess such properties. Metchnikoff, Nuttall, Fodr, Lubarsch, Vaughan and Novy, and a host of others, have published most interesting works on this subject. From their several experiences we may safely draw the following conclusions: The normal human blood possesses bactericidal power, varying in degree in its antagonism to different microorganisms; the microbe-destroying substance is found in the serum, but is produced by the leucocytes; certain chemical changes in the blood may be induced either to increase or diminish its bactericidal power, and this property of the blood naturally diminishes after the clot is forty-eight hours old.

Nuttall, following the suggestion of Metchnikoff, was probably the first to demonstrate the bactericidal power of normal blood serum. Working under the direction of Flügge, in 1888, he used defibrinated blood taken from various species of animals and found that this blood destroyed the *Bacillus anthracis, Bacillus subtilis* and the *Staphylococcus pyogenes aureus* when brought into contact with them. He also confirmed the finding of Fodor that after a while the blood loses its germicidal properties and becomes a suitable culture medium in which germs grow abundantly.

The fact having been thus determined that the blood serum removed from the body acts far more rapidly and energetically on microbes than the plasma and lymph within the body, the disparity of action was further shown by Lubarsch (Allbutt's System of Medicine, Vol. I, p. 89) who attempted to ascertain the exact power of the blood of some animals over a given serum; using the bacillus of anthrax and experimenting on rabbits he injected known quantities into the circulating blood and found that this animal was quite able to take care of a dose of less than 16,000 germs, but if a larger number were injected fatal infection resulted. If he drew a small quantity of blood from an animal of the same class and size into a test tube and inoculated that with the same microorganism, many times that number of germs were destroyed. Then a most interesting series of investigations followed to determine what element of the blood possessed this bactericidal quality and how it acted. Vaughan and McClintock (Cellular Toxines, Fourth Edition,

1902) have presented the most conclusive report on these points and they hold that the leucocytes secrete some substance which is poured into the serum, that this substance is a proteid, and that the only proteid likely to be present in blood serum to which such properties could be attributed is nuclein.

The clotted blood possesses greater power than the circulating blood probably because in the formation of the clot the leucocytes break down and discharge their entire complement of this nuclein. Other workers have demonstrated the transient duration of this power in the blood-clot, a power which seems to diminish rapidly after forty-eight hours, and the fact that certain chemical changes in the clot may cause a variation of its power. The bactericidal power seems to be present in freshly drawn blood only when it is alkaline in reaction. If its alkalinity be raised above normal the bactericidal power will be somewhat enhanced, but if the blood be below normal alkalinity, or if it be rendered acid in reaction, such power is diminished or actually destroyed. The nuclein acts only in an alkaline serum. Again, if alcohol be added to the blood, the bactericidal property is destroyed through the precipitation of the albuminoid constituent. Bichloride of mercury, likewise, has a deleterious influence on the bactericidal properties of blood serum.

These chemical experiments, it may be said in passing, have an important bearing on the use of the blood-clot as a surgical dressing. The use of carbolic acid and alcohol for the cleansing of the wound, as an extra precaution of cleanliness prior to the introduction of the blood, has been recommended by some surgeons, but it seems not unreasonable to venture the suggestion that some of the failures with the blood-clot dressing may have been due to excessive zeal in the use of carbolic acid and alcohol for antiseptic purposes. If exact neutralization were possible and the wound left in a neutral state, no harm could result from the employment of these substances, but if there be left any measurable quantity of either it militates against success. On theoretical grounds it would appear more rational to rely on dry cleansing of the wound with instruments and sterile sponges or to wash the cavity with sterile salt solution which, if it produces any effect on the coming clot, renders it more alkaline and increases its power to control septic material.

4. Clinical Evidences in Support of the Method.

The author has been one of the most enthusiastic followers of Dr. Blake in the employment of the blood-clot dressing, even going further than the *master* would have advised; very little effort has been made to select the cases but, on the other hand, the blood-clot has been employed almost as a routine measure and upon all kinds of cases in order to determine its limitations, if there were any. The wounds have always been sutured tightly, without any provision whatever for drainage, sometimes with interrupted silk or catgut, occasionally with metal clamps, most commonly with subcutaneous silver wire suture. It mattered not in many of my cases that the amount of pus collected over the mastoid (subperiosteal abscess) had been excessive or that the entire cellular structure had been necrotic, nor indeed, that the sigmoid sinus or cerebral dural covering had been exposed by the disease or the operator; closure under blood-clot was frequently performed under such circumstances and numerous cases which looked utterly hopeless resulted in primary healing. In spite of trying it in these extreme cases and taking the most unusual chances, where the clot would be expected to break down, I have secured the highest percentage of successes. In a paper read before the American Otological Society in 1906 (Tr. Am. Otol. Soc., 1906, p. 385), I reported one hundred cases of mastoidectomy in which the primary healing of the mastoid wound was obtained in 72 per cent of cases, where the disease was the result of acute suppurative otitis media, and in 50 per cent of the cases that had originated in chronic purulent otitis. During the three years that have since elapsed not only has this high percentage of successes been maintained but improved upon. Between September, 1908, and May, 1909, my associate, Dr. Jesse W. Downey, Jr., and I had 16 consecutive primary healings; the 17th case, one of my own, broke down; this being all the cases operated upon by us in one institution, the Baltimore Eye, Ear and Throat Hospital, during that period. These were not selected cases but embraced all that came into my service in that institution and varied in character from simple mastoiditis limited to the antrum and neighboring cellular structures, to cases presenting extensive destruction of the cortex, exposure of the dura over the antrum and tympanic cavity, or of the sinus dural wall, and invasion of the soft tissues of the neck. The technic and team-work developed by us possibly accounts for our high percentage of successes but I could name many other operators who are securing very satisfactory results.

5. The Technic which Gives the Greatest Assurance of Primary Union in Blood-clot.

While Dr. Blake in his earliest reports on the use of this method called attention to the necessity of doing a very thorough operation, under strict aseptic precautions, if one would expect success, and while I have always felt that thoroughness in the removal of any possibly infected material and the nearest possible approach to an aseptic technic throughout every stage of the operation were of the greatest importance in the attempt to secure primary union of the wound, I was unwilling three years ago to attribute my own success entirely to good technic. To have done so would have seemed too much like a criticism of other men's methods and I had no reason to assume that my technic was materially different from that of others. During the past few years, however, my opinion on this point has somewhat changed. Close observation of the work of others as well as careful introspection has shown me that there are many opportunities for small differences in the work of men who think they are following the same technical rules. It is just these little things that lead very often to failure. There is nothing about the technic employed in the hospital where most of my work is done that is not recognized and endorsed by all surgeons and supposed to be a matter of routine with most of them. Insistence upon perfection in the details, accompanied by the enthusiastic assistance of my associates, is, possibly, the

main point of advantage in my service. Every one of my assistants is as anxious as am I to bring about a satisfactory result and rejoices with me over a primary union; many times I have found their hints helpful and they are encouraged to look out for errors in technic and to suggest improvements looking to greater facility or safety in the work; when one of them operates I serve as assistant and, by thus working together, my brother, Dr. J. N. Reik, Dr. Downey, Miss Dick (the Superintendent of Nurses), and I have developed a systematic procedure and a team-work which, I think, may account in large measure for our success.

It may not be amiss to briefly describe the preparation for, and conduct of, a mastoidectomy as performed in the Baltimore Eye, Ear and Throat Hospital:

Preparation of Patient.—Whenever possible we prefer to have the patient in the hospital at least over night and to operate early in the morning. The hair is cut and shaved from the scalp over an area which extends at least 3 cm. above and 6 cm. behind the auricle. This shaven area, together with the auricle, cheek and neck, down to the clavicle, is scrubbed with soft soap and water, using a stiff hand brush. All the soap is then removed by flushing the surface, including the external auditory canal, with warm sterile water. The surface is then mopped with gauze sponges soaked in a saturated solution of potassium permanganate and then the stain, thus produced, is removed by similar mopping with a saturated solution of oxalic acid. This is followed by a thorough rinsing of the whole area with a warm solution of mercury bichloride in the strength of 1-2000. A large pad of moist bichloride gauze is now laid over the entire field and a bandage applied to hold it tightly in position until the hour for operation. After anæsthetization the patient is placed on the operating table, a sterilized Kelly pad, covered with sterile towels, under the head, and the bandage and outer layers of gauze are removed. If the patient be a woman a sterile rubber cap is now put in place to protect the hair and to hold it as much as possible out of the way. A folded towel is laid over the face, vertically, in front of the auricle and a wet bichloride towel is then wound about the head, binding the upper end of the first towel in place and completely enclosing the rubber cap, in such a way as to leave only the auricle and mastoid region of the head exposed; a large sterile sheet, enveloping the patient's body and overhanging the table, having been drawn up to the chin and tucked under the shoulders. By a special frame-work attachment to the operating table, a smaller sheet having a central, circular opening of 15 cm. diameter is suspended over the patient's head, so that when fastened with safety pins to the towel over the face the patient's face and the anæsthetizer are absolutely shut off from the operation field and every portion of the patient and table is hidden save the field of operation as viewed through the opening referred to in the sheet over the head (Fig. 1).

Preparation of Instruments.—All the instruments selected for the operation, except knives and scissors, which are boiled separately, are wrapped in towels and boiled in soda solution and such packages are transferred to the instrument table unopened. One large and two small glass or metal topped tables are employed. The large table is covered with sterile towels and the surgeon or the instrument nurse unrolls the packages of instruments and spreads them out in a convenient way so that no time shall be wasted by the surgeon in searching for the next instrument required. One of the small tables is covered with a sterile towel and upon this are placed the sponges, sponge forceps and artery forceps that may be required by the assistant. The second small table supports two sterilized dishes, one containing carbolic acid solution and the other sterile water; the nurse stands behind this table to receive instruments from the surgeon after they have been used and with sterile gauze sponges wipes each instrument clean in the carbolic acid solution and rinses it in the water dish before replacing it upon the instrument table; this nurse goes through the same preparation for her duties as does the surgeon and assistant and sees that no instrument, once used, is taken up again until it has been cleansed (Fig. 2). During the interval between preparation of the instruments, sterile solutions and sponges and the moment of beginning the operation all of this paraphernalia on the tables is covered by sterile towels for protection.

Preparation of the Operator and his Assistants.—The surgeon and assistant remove all of their outer clothing and, over a sleeveless undershirt and drawers, put on sterilized white duck sleeveless shirt and trousers. Sterilized white canvas shoes replace the ordinary foot wear. The hands and arms, to a point above the elbow, are then scrubbed vigorously with a stiff brush, green soap and water for five minutes, particular attention being given to the finger nails. After rinsing in clean water the hands and arms are stained to the elbow in a saturated solution of potassium permanganate and then immersed in a saturated solution of oxalic acid until decolorized. Immersion in a 1-2000 bichloride of mercury solution for five minutes follows, and then a long-sleeved sterile gown, fitting tightly at the neck and enveloping the body to the knees is donned. A sterile cap is placed upon the head to entirely cover the hair and reach down on the forehead nearly to the eyebrows, and a gauze mask is placed over the face and tied behind the head so that only the eyes are visible. Rubber gloves that have been boiled are now drawn onto the hands while held immersed in bichloride solution (Fig. 3). Except for variation in garments, the same procedure is followed by the physician and nurse who are to assist the operator. If a head-light is to be worn, it, together with all connecting cords, is sterilized in a formaldehyde gas apparatus of the author's invention and put on over the cap when required.

Operation.—The details of operating need not be described; they vary in no important respect from those in general vogue to-day. The prime object is, of course, to thoroughly remove all necrotic or diseased bone and every particle of septic material. The aim is completeness and if there be any doubt as to the condition of tissue under inspection we prefer to consider it as probably inflamed or infected and to remove it, there being less danger of making an operation too extensive in these regions than of failing to completely eradicate diseased structures. Feeling that we have succeeded in this feature of the

FIG. 1.—Protection of the operation field. Anesthetist completely shut off.

FIG. 3.—Costume of the operator and protection of the field. The whole designed to render it impossible for anything not sterile to come into contact with the wound area.

FIG. 2.—Cleansing of used instruments by a clean nurse; so that no visible particles of infective material can be carried back to the wound.

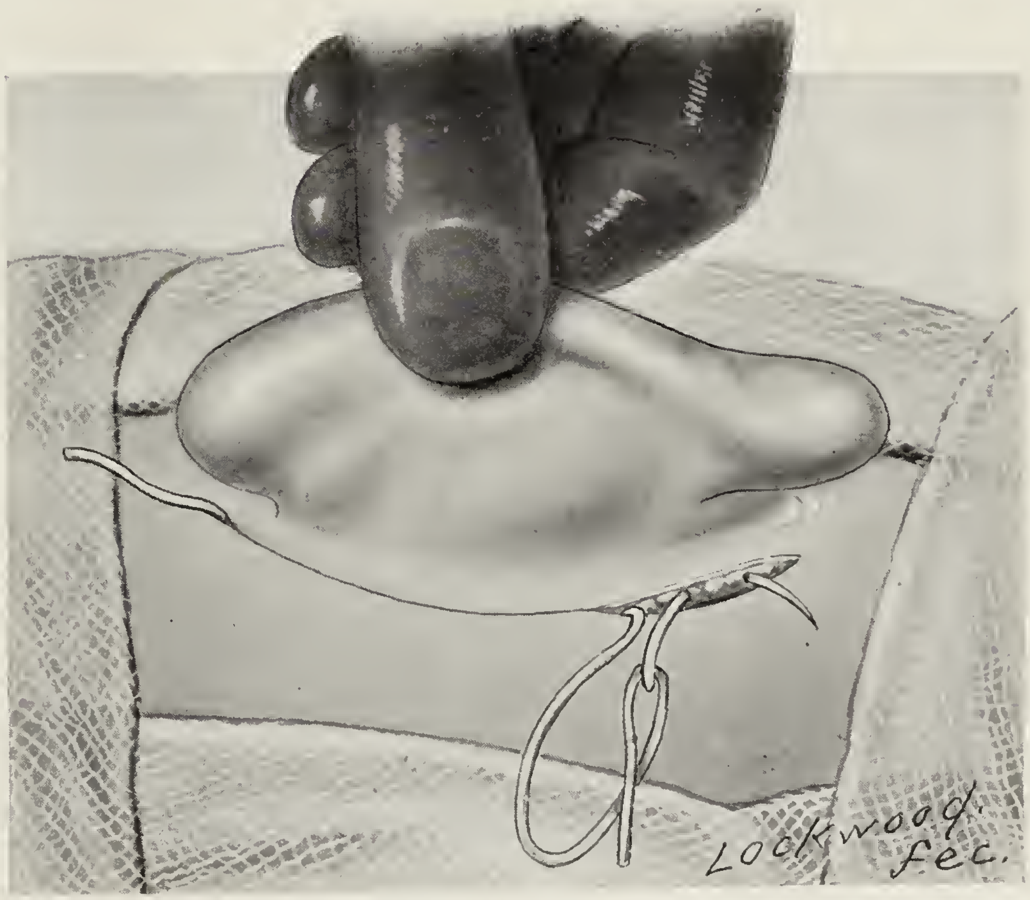

Fig. 4.—Primary closure by subcutaneous silver wire suture, after blood-clot dressing.

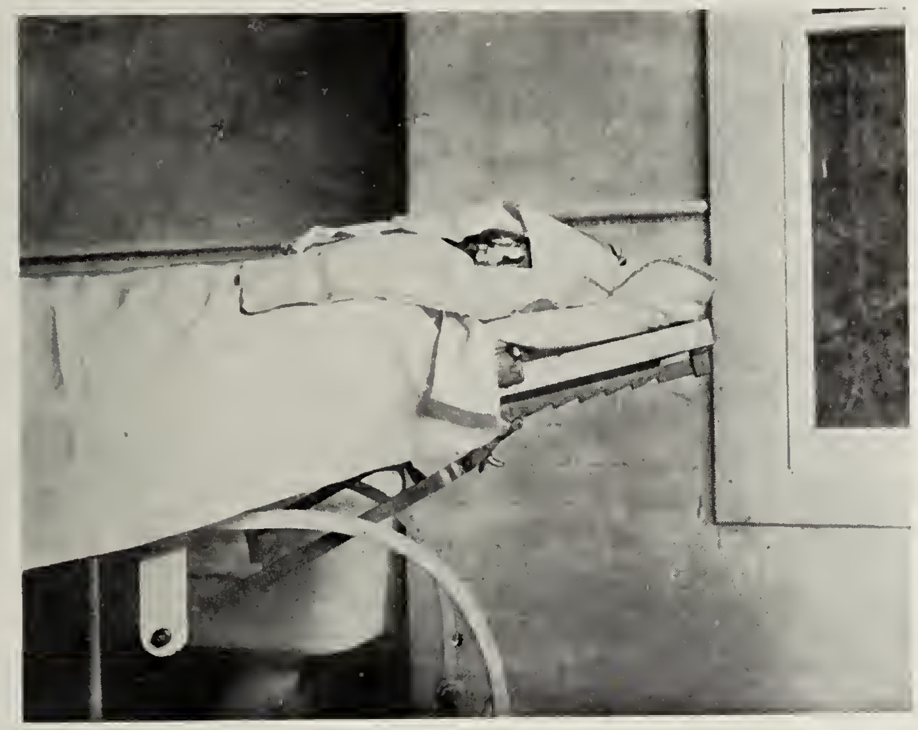

FIG. 5.—First dressing; fifth day after operation. Gauze dressings have been removed, but silver foil is still in place.

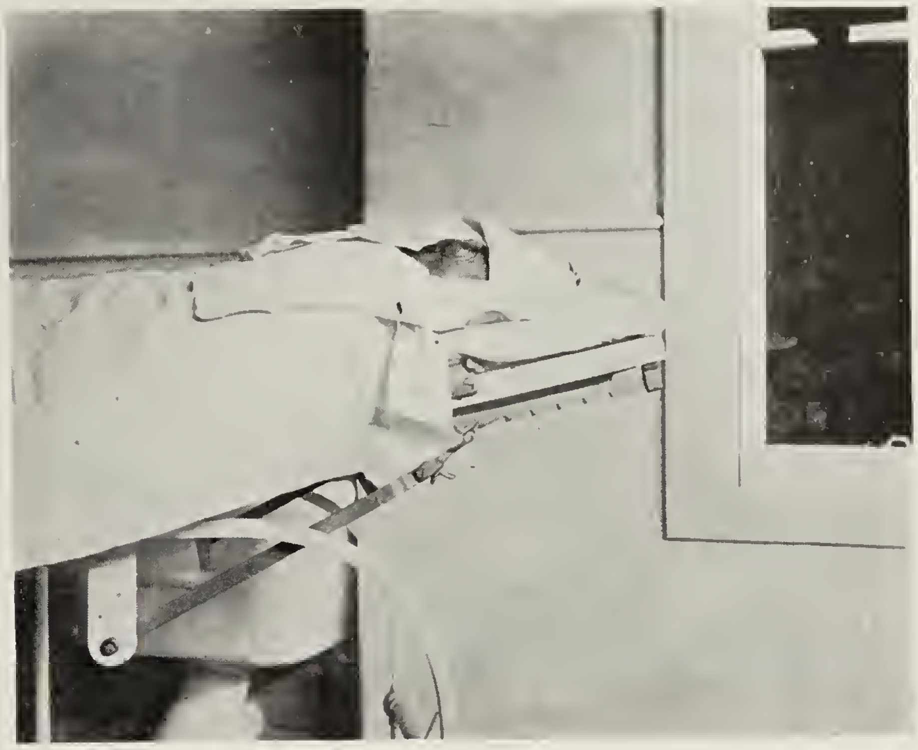

FIG. 6.—First dressing; fifth day after operation. Silver foil removed. Primary union.

FIG. 7.—Three weeks after operation. Practically no scar; the line of incision barely visible.

operation, the wound is irrigated with hot normal salt solution and fresh sterile towels are placed all about the operation field to cover the towels or sheets that have become soiled; occasionally we find it necessary to remove the first towels and sheets and to replace them with clean ones, to better assure a clean working field. Having dried out the wound cavity by mopping away the salt solution with sterile pledgets of gauze it is permitted to fill with blood and the edges of the incision are brought together neatly by a running subcutaneous suture of silver wire (Fig. 4). Ordinarily the oozing blood from the soft tissues that follows irrigation and drying by rubbing with gauze is quite sufficient to fill the cavity; if this should not happen it is an easy matter to provoke a slight hemorrhage by scraping the wounded subcutaneous tissues with the scalpel. Over the sutured wound, care having been taken to get nice coaptation of the edges, several sheets of sterilized silver foil are carefully laid and upon this a dressing of dry sterile gauze, in thin layers, is built up and the whole covered and held in place by a roller bandage. Unless there is some necessity arising for doing so, the bandages are not touched again for five days. Then, the dressings may be removed, the suture withdrawn and, if the wound has held, a layer of sterile gauze is applied and held in place for a few days by a protective bandage until union is firm.

After Dressings.—Should the clot become infected and break down it will almost surely be indicated by a continuance of the fever, by a return of febrile condition about the third day or by evident soaking of the dressings. I do not believe it is possible to suture such a wound so tightly as to prevent the escape of accumulating secretions; in other words, once you have made an opening into the mastoid that incision remains the direction of least resistance for inflammatory products. Not infrequently a case which has been running a high temperature prior to the operation will continue to show fever, usually of lesser degree, for the two or three days succeeding operation but that is not to be interpreted as due to infection of the blood-clot; it is the systemic fight with already absorbed toxines. Again, in milder cases, a temperature of 99° F. or 99.5° F. for 48 hours after such an operation is of no consequence and may possibly be due to some reaction not fully understood that accompanies healing under bloot-clot; at least, I have frequently observed that condition, and it in no way affected the result of primary union with perfect and permanent recovery. If the temperature, after 24 hours has elapsed, runs above 100° F. you may inspect the wound, but, otherwise, steer clear of the desire to meddle unnecessarily with the dressings. Should you find at the time of first dressing that pus is escaping from the incision, withdraw the suture, irrigate the wound and, if necessary, pack with gauze. Sometimes there will be simply a little superficial breaking of the clot and it will not be necessary to remove the entire clot or pack the wound; perfect primary union will not be the result in such cases but the period of granulation and healing by secondary intention will be greatly facilitated by leaving so much of the clot as has held firmly. When complete destruction of the blood-clot occurs and the entire wound has to be cleansed and packed the patient has lost practically nothing by the attempt to secure primary healing and the case will proceed exactly as it would have done had packing been resorted to originally (Figs. 5, 6, 7).

Finally, let me appeal to you to give this method a trial. Numerous operators have now demonstrated its practicability and we have shown that it was possible to secure primary union in 90 per cent of our last series of cases; even should you succeed in no more than 20 per cent of your attempts you will still have scored a triumph in surgery because for those few patients you will have greatly lessened the period of convalescence and secured the best cosmetic results to say nothing of the discomforts avoided.

THE PRESENT ATTITUDE OF THE TUBERCULOSIS NURSE TOWARDS HER WORK.

By Ellen N. La Motte.

Tuberculosis Nurse: Instructive Visiting Nurse Association of Baltimore.

The attitude of the tuberculosis nurse towards her work has undergone a complete change during the past five years. In order to know the reason for this change, we must know the attitude of the nurse in 1904. Her opinion at that time was but a reflection of that of the general public, which had been somewhat hastily and optimistically informed that tuberculosis was a curable and preventable disease. (That this could be accomplished only under ideal conditions was not mentioned.) The consumptive failed to recover because he was ignorant—he spread the disease because he was ignorant, and to dispel this ignorance, therefore, by careful house-to-house visits of instruction was the mission of the tuberculosis nurse.

The nurse of five years ago was as ignorant about tuberculosis, however, as is the average nurse of to-day. I will not say more so—at least as ignorant. The nurse just graduated from a training school has but the most elemental ideas in regard to tuberculosis, but it is not her fault. No hospital will admit such patients, and she has no way of seeing them. When by chance a consumptive is admitted to a ward, he is turned out again as promptly as his condition will allow. Such casual acquaintance with typhoid fever, for example, would not equip a nurse in any practical manner to deal with it, yet we somehow expect nurses to possess a degree of information about tuberculosis that is carefully denied them. One person more hopelessly ignorant than the average nurse is the average medical student or doctor. Yet to these two classes of people,

whom the hospitals do not properly equip, do we turn for light and leadership in the anti-tuberculosis crusade.

The nurse of five years ago, therefore, began her work with little or no knowledge of her subject. To her it was a vague medical problem to which certain platitudes were applicable. That it was a social problem, and a social problem alone, was utterly beyond her. Her ideas were about as follows: Tuberculosis is a curable and preventable disease. All that was necessary was to explain this fact to the patients, and they would live their lives accordingly. Milk and eggs are good for consumptives. If the patients were too poor to buy them, let them be supplied by the charity organization. The disease is spread by means of the sputum. The careful consumptive is not a menace. This equipment was very simple but very logical. It was merely a question of repeating this often enough to the patients to make the required impression. It was merely necessary to state an obvious truth, and results would follow.

It is an interesting fact to note that all tuberculosis work in a community begins in just this way. All new nurses, all new dispensaries, all new anti-tuberculosis societies, go through this stage. Unfortunately it takes several years to pass through it. The present attitude of the lay public to-day has not progressed beyond this view-point.

This, then, being the way the nurse began her work, her stages of progress were as follows: She attempted to educate her patients, and she herself became educated. She found that simply telling people what to do and how to do it, was not in the least synonymous with having them do it the minute her back was turned. She found that most of her teaching was disregarded—her patients careless, grossly careless, yet often with the blandest confidence that they were doing the right thing. She found intelligent people stubborn, and ignorant people so crushed by circumstance, so handicapped by poverty and conditions that they were unable or unwilling to follow advice. In certain conditions she appealed to the charity organization for aid, and got it—in inadequate amount. But this is right—it is not the function of the charity organization to abolish disease, and lavish relief (could such a thing be obtained) is not the way to stamp out tuberculosis. A great step forward is made when a nurse realizes the folly of asking for milk and eggs for a patient whose whole character and manner of life preclude the chance of recovery. As far as benefit to the patient was concerned, she found but temporary results. By means of her teachings, some few patients were enabled to "get along" in a more or less hap-hazard fashion. Of course an absolutely starved patient *does* gain a few pound if he is fed properly for a few weeks. But for the most part this gain is but temporary.

Many nurses leave the work too soon—they give it up at the end of a year or so, having acquired certain half truths which they disseminate among a gullible public and do great harm thereby. For instance John Smith makes a gain of twenty pounds in a few weeks and returns to work. At that point the nurse leaves the work but continues to talk about John Smith, and the charitable agency calls attention to its wonderful constructive work in having supplied John Smith with the milk and eggs which enabled him to return to work after having gained all those pounds. Could John be followed a year longer, however, he would be found able to work only two days a week, and his eldest daughter would have become infected. Another year, and John is sitting around the house all day, while his wife is at work, and another child has contracted the disease. The public's attention is not called to that sort of constructive work, however. It seems a policy of doubtful wisdom to enable a certain number of patients to "get along" for a period of months or years—working part of the time, sick part of the time, yet spreading the disease all the time. Prolonging a center of infection, while not at the same time producing adequate carefulness, is not a solution of the tuberculosis problem.

Much has been written about the sanatorium as an educator. When it comes to educating the very poor, the class of patients with which the nurse deals, the sanatorium is as ineffectual as she is. The sanatorium is useless for poor people—for them there is no cure. Unless the means of life are at hand in such abundance as to procure freedom from worry, rest, good food, shelter and clothing, the sanatorium avails the patient nothing. His discharge into an environment that he cannot control, means relapse. The sanatorium as an educator is as nothing compared to the tearing down of such "education" by crushing poverty and degrading living conditions.

During the first year that the writer did tuberculosis work, from June, 1905, to June, 1906, she personally visited 521 patients. Not a few times, but over and over again. Of that number 283 have since died. So much for the personal benefit to the patient. There have been 132 lost. They moved out of the city, or their addresses became lost in various ways. What has become of them is unknown. There are still 106 patients on our visiting list to-day, living after a period of five years' careful instruction. I should not call them well, but they can get along after a fashion, and any sanatorium would be proud of them. The degree of health they possess would not satisfy you nor me, but it satisfies them. These 106 patients, however, whom we have taught so carefully how to live and how to protect others, have succeeded, in spite of all we could do, in spreading the disease to 64 other people, who are now also on our visiting list to-day. In other words, these 106 patients whom we have so carefully instructed, have spread tuberculosis among sixty per cent of their number *that we know of*, and what they have done to other people *whom we do not know* is a matter of conjecture. These sixty-four people were all apparently well when we began to visit the original patients five years ago, and they have all of them contracted tuberculosis apparently within the last two or three years. Of course there may have been other avenues of infection through which the disease was contracted, but from the point of view of a nurse, these sixty-four patients had ample opportunity of contracting tuberculosis from sources with which we know them to be in daily contact. And it is reasonable to suppose that the 132 patients whom we lost, if they are still living, are also keeping up their share of destruction. But the question, however, is

with these carefully taught patients, who were not ignorant and whose families were not ignorant of the nature of their disease. Further comment is unnecessary.

We feel, therefore, those of us to whom continuity of service has given a broad horizon and experience, that the home is not the place for a patient with tuberculosis. In spite of the utmost teaching, and in spite of the utmost cooperation, there are a hundred reasons due to poverty, environment and temperament, that nullify all attempts at adequate carefulness. The patient cannot be properly careful in his home life, and the element of danger to his family and the community is ever present. In homes of the class we visit, the technique of the sanatorium cannot be applied.

What then is the present attitude of the nurse to tuberculosis work and what is her value to the community? Her chief value lies in her ability to put facts before the public. If for no other reason than just this alone—her conviction of failure in the direction from which so much was expected—she would have justified her existence during the past five years. She can teach in the homes and see the futility of her teaching—she can send early cases to a sanatorium and see the futility of their cure—and she must be forced to realize that a community with such a disease in its midst has but a flimsy protection in an "education" that is disregarded, no matter for what cause.

She must now be regarded, not as the end, but as the means to the end. The end of the question lies in the establishment of large and comfortable hospitals for advanced cases, and a segregation that would be for the most part voluntary. Hundreds and hundreds of advanced cases have begged in vain for admission to our sanatoria. Could they have been admitted, we should have had no further early cases. When a doctor examining an applicant, says to a nurse "All these cases are too advanced—can't you send me some nice early ones," and she replies, "Yes, in about six months I'll have a lot," the situation becomes absurd.

The work of the nurse to-day does not mean prevention nor cure, except in a certain small proportion of instances. She is, however, an educator of the first rank, but her mission is to educate people with tuberculosis to go out of their homes rather than stay in them. She can discover cases, bring or send them to dispensaries for diagnosis, instruct as to fumigation, and cleaning, give nursing service to ill patients, but above all she must teach the patients to go into hospitals that an enlightened public must provide.

CORRESPONDENCE.

Editor Bulletin of the Johns Hopkins Hospital.

Sir.—In view of the recent work of Col. C. T. Woodruff, of the U. S. Army Medical Corps, "Expansion of Races," reviewed in the January Bulletin, it is interesting to note the great Australian experiment in the use of white labor in tropical agriculture as detailed in the following extracts from "The Nineteenth Century and After" for February, 1910:

"'The attempt to acclimatise the white man in the tropics must be recognized to be a blunder of the first magnitude. All experiments based upon the idea are mere idle and empty enterprises foredoomed to failure.' Thus in 1898 wrote Mr. Benjamin Kidd in his 'Control of the Tropics' (p. 48), and his opinion was supported by the emphatic pronouncements of many other authorities. Nevertheless, in 1901, the Australian Parliament passed a law—the Pacific Islanders Act—which prohibited the employment in Australia of indentured coloured labourers, and rendered the Australian sugar plantations dependent on white labour. It thus staked the existence of an important industry, and the loyalty to the Commonwealth of the second largest of its States, on the success of a new and daring policy. The Australian experiment is the greatest practical attempt yet made to solve the problem whether the waste spaces of the tropics can be developed as white colonies instead of as black dependencies."

"A Royal Commission upon the Queensland Sugar Industry in 1889 had reported that for the area north of Townsville 'there was absolute unanimity amongst all the witnesses examined that white men could not cultivate cane,' and it quoted such opinions as 'withdrawal of black labour means shutting up the northern districts,' and that in those areas for 'five months in the year whites cannot work.'"

"The majority of the Commission declared 'it to be our opinion that if all coloured labour be withdrawn from the plantations, the extinction of the sugar industry must speedily follow, and we therefore recommend that the introduction of Polynesian labour be permitted to continue at all events for some years longer than the period now limited.'"

"According to Sir Malcom McEacharn the death-rate of the Kanakas from 1891-1895 was 42.73 per 1000 per annum; from 1896-1900 it was 30.08 per 1000. In 1902, at Mackay, it was 26 per 1000, and in 1903 about 32 per 1000, whereas among the white population, in spite of infant mortality and deaths from old age being included, it was only 12 per 1000."

"It has been said that though men may withstand the climate it is so injurious to children that they grow up feeble and degenerate. On inquiry at the Education Department at Brisbane I was informed that 'there is no indication in the inspectors' reports that the Northern children are less industrious or less fit for a long day's work than those in the South.' Such evidence shows that the white children of tropical Queensland are not weak, anæmic degenerates, while the increased output of sugar since the deportation of the Kanakas shows that white men are willing and able to work there."

"It may be thought that white labour has not yet been used long enough to have passed out of the experimental stage, but it has unquestionably already falsified the forecasts of inevitable ruin, and allayed the fears of many who believed that white men could not do agricultural work, nor their families thrive, in such an ultra-tropical climate as prevails along the coastlands of tropical Queensland."

It is evident that we need more testimony of this character before the question can be considered settled.

George M. Gould.

Ithaca, Feb. 25, 1910.

PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS MEDICAL SOCIETY.

December 20, 1909.

Dr. Louis Hamman in the chair.

I. Exhibition of Specimens and Cases. Dr. G. L. Hunner.

Dr. Hunner exhibited two interesting gynecological specimens. The first was that of a large fibroid of the uterus which had undergone malignant changes. In this particular case there was no particular complaint other than the size of the mass which simulated a well advanced pregnancy, there was no pain and very slight discomfort.

The second specimen was a large ovarian cyst with a twisted pedicle. This patient had suffered with three sharp attacks of pain in the region of the appendix.

II. Nitrous-Oxid-Oxygen Anæsthesia by Means of Rebreathing and Various Therapeutic Uses of Rebreathing. Dr. Willis D. Gatch.

This paper will appear in a later number of the Bulletin.

III. Report of a Case of Strongyloides stercoralis with Marked Eosinophilia. Dr. W. A. Baetjer.

This case of strongyloid infection is reported chiefly on account of the high grade of eosinophilia occurring in a case of intestinal parasitism. Strongyloid infection itself is apparently quite uncommon in this country, only fourteen cases having been reported up to the present time, the first by Strong in 1901. Six more cases are to be found in the Johns Hopkins Hospital statistics which together with this case makes a total number of twenty-one cases in all.

The patient is a young girl of twenty-two years, who entered the hospital on December 7, 1909, complaining of shortness of breath and swelling of the ankles and feet. Her personal and family history is entirely negative; she has always lived in Maryland and has never been out of the State.

The onset of her present illness dates back to July, 1907. Since that time she has had recurring attacks of dyspnœa and weakness but no diarrhœa or intestinal symptoms of any kind. Her physical examination revealed only an extreme pallor of the skin and mucous membranes. The examination of her blood showed 4,186,000 red corpuscles, 11,400 leucocytes, and 30 per cent hæmoglobin (Sahli). Differential count:

Polymorphonuclears	30.5 per cent.
Eosinophiles	45.0 "
Lymphocytes	23.0 "
Large mononuclears	6.0 "

The eosinophile count in this case is higher than in any other case in the hospital statistics except the counts reported by Brown in cases of trichinosis.

Examination of the stools showed numerous actively motile rhabditiform embryos which on incubation changed directly into the filariform larvæ and in no instance could the free living sexual forms be cultivated. No adult worms or eggs were found. On account of the frequent association of uncinariasis with this infection, sedimentation methods with salt solution and the method described by Bass were tried, but without results. The direct metamorphosis of the rhabditiform into the filariform larvæ has been the rule in all these cases, the sexual forms having been grown in but one of the cases in all the twenty-one collected. The ova were found in four cases but the adult female in none. A moderate grade of anæmia was found in most of the cases although this is hard to estimate owing to the number of cases presenting complications, but in no uncomplicated case was there noted a chlorotic anæmia as marked as in the present instance.

Of the twenty-one cases collected, ten were natives of or had lived in one of the tropical countries, four came from the Southern States, while three of the other seven had never been out of the State of Maryland.

The most striking feature of the present case, however, was the marked eosinophilia of 45 per cent on the day of admission. Of the cases reported thus far there was an eosinophilia in five, the percentages varying between 6 and 13 per cent, except in one case in which these cells constituted 38 per cent of the white blood cells. In several of the cases of strongyloid infection with eosinophilia, it has been noted that these cells have decreased in proportion as the symptoms abated and after the administration of tæniafuges, the decrease being associated with a concomitant rise in the proportion of polymorphonuclear cells. A similar observation was made some years ago by Brown in the cases of trichinosis.

This observation is well illustrated in the present case in which the eosinophiles counted after the administration of three courses of thymol (ʒii) had dropped to 10 per cent with a simultaneous increase in the polymorphonuclear cells from 30.5 to 55 per cent. Since the second course of thymol over three weeks ago no parasites have been found although the stools have been examined daily. The patient's hæmoglobin which was 50 per cent on admission has now risen to 85 per cent and she is apparently rid of her infection.

IV. Demonstration of a Method of Producing Normal and Abnormal Heart Sounds for Teaching Purposes. Dr. C. W. Larned.

This paper appeared in the Johns Hopkins Hospital Bulletin for February, 1910.

January 17, 1910.

Meeting of The Johns Hopkins Medical Society, Dr. Louis Hamman in the chair.

I. Experimental Poliomyelitis. Dr. Simon Flexner.

In 1907 Dr. Flexner first began his studies on Experimental Poliomyeletis and attempts at that time were made to transmit the disease to the lower monkeys.

Owing to the fact that access was not possible to a single fatal case of the disease during the years 1907 and 1908, work was done only with the fluid obtained from the spinal canal

and this fluid seemed incapable of setting up any recognizable pathological condition when inoculated into laboratory animals including the monkeys.

In 1909, however, material was obtained from two fatal cases of infantile paralysis in human beings, the first dying from five to six days after the appearance of the paralysis, the second four days after the onset of the disease.

In one of these cases the entire spinal cord was obtained twelve hours after death and inoculated into animals, four hours later. The virus was obtained by making an emulsion in salt solution of the spinal cord.

In order to favor the transmission of the disease to monkeys the brain was chosen for the site of inoculation, which was made under ether anæsthesia, through a small trephine opening. In the careful study of 81 monkeys inoculated successfully with the virus of epidemic poliomyelitis we find the following features present.

Incubation period was calculated from the time of the inoculation to the onset of definite symptoms of the disease. The shortest period being four days the longest thirty-three days, the average about nine days.

Prodromal Signs.—When the virus is inoculated directly into the brain or other parts no immediate effects are produced. From six to forty-eight hours later, the animals become nervous and excitable and a slight tremor of the head, face and limbs can be noticed. The temperature does not rise constantly during the incubation period and gastro-intestinal symptoms rarely occur.

Onset of Paralysis.—The development of the paralysis is sudden and the muscles first involved are generally the larger group of the voluntary muscles. The muscle groups of both legs were involved in 20 monkeys, the right leg alone in 8 cases, and the left in 12 cases. Both arms in 3 cases and the right and left arm alone in each of 9 cases. Eight cases showed bulbar or cerebral paralysis. Marked spasticity of the limbs and incoordination, epileptiform convulsions with tonic and clonic muscle spasms and finally sudden death of apoplectiform type. When cerebral symptoms appear death follows usually within half an hour.

The paralysis extends quite rapidly from one group to another, in some mild cases the transition may pass unnoticed but in severe cases the passage is rapid from one limb to another, to the back, and the neck, until death ensues.

The termination of the disease is not always fatal, the affected monkeys may recover, the paralysis reaching a maximum, remains stationary and then recedes. Usually within a week in the mild cases, the animal regains its health and general strength except for the actually paralyzed muscles.

In those animals which die, the force of the affection is directed upon the medulla early in the disease, and death may occur within a short time after the appearance of the first symptom.

The Nature of the Virus.—Though the microorganisms of poliomyelitis cannot be affirmed at present many interesting facts concerning the nature and resistance of the virus have been determined. Film preparations and sections from the human and monkey's spinal cord have shown no bacterial or protozoal parasites. The filterability of the virus has been demonstrated and these bacteriologically clear filtrates have been used repeatedly to inoculate monkeys. From the inoculated monkeys the virus has been transferred to other monkeys and has regularly caused paralysis. The virus of poliomyelitis, in common with the filterable viruses of other diseases is resistant to injurious agencies. It will retain its virulence on being kept frozen at —2 to —4° C. for at least 40 days and will keep at least 50 days at a temperature of +4° C. The virus will resist glycerination for at least 7 days and resists drying over caustic potash in a dessicator for the same length of time.

The virus is readily injured by heating, a temperature of 45°—50° C. maintained for one-half an hour will render the filtrate incapable of producing paralysis. The results of the attempts at cultivating the virus of poliomyelitis in test tubes are in doubt.

The question of immunity also is not settled, although in experiments a period is found immediately following an attack of poliomyelitis during which the monkeys are refractory to reinoculation with the active virus. Just how enduring the immunity is, is still to be determined.

There is no reliable way of estimating, the virulence of the virus, since the number of the organisms inoculated is not subject to control. There are many avenues for transmitting the virus to the central nervous system of the monkeys and it is of prime importance to determine the portal of infection in man.

The lymphatics of the nasal and pharyngeal mucosa through the cribiform plate forms the most direct connection existing between the meninges and the external world. It has been possible on account of the filterability of the virus, which process would eliminate all bacteria, that the virus may escape from the meninges by this route. The accomplished infection by this route is still to be determined. It can be assumed that the monkey is relatively unsusceptible and hence difficult to infect through the natural channel. The lesions in the spinal cord and medulla of the monkeys, visible to the naked eye, consists of congestion and hemorrhage into the gray matter chiefly, but not exclusively confined to the anterior horns. The general appearances of the spinal cord, medulla and brain are not greatly altered, and the visible effects are no proper measure of the damage inflicted by the virus.

Microscopically, however, the vascular lesions are found to be the primary causes of the lesions of the nervous system, the severity of which is determined by the particular vessels affected and the intensity of the involvement.

No part of the spinal cord is spared and the medulla probably never entirely escapes injury. The degree of affection is determined by the richness of the arterial blood supply, whence is explained the liability of the lumbar and cervical enlargements to severe lesions.

Discussion.

Dr. L. F. Barker.—Those of us who see cases of this disease clinically in human beings must be much impressed with the experimental studies of Dr. Flexner. One feature of acute

anterior poliomyelitis which is discouraging to clinicians is the sudden onset of the paralysis (usually in maximal intensity and distribution) without forewarning sufficient to permit one to suspect the nature of the infection. Since the damage is done before a diagnosis can be made much more is to be hoped from preventive measures than from therapy. The greatest hope for prevention lies in such experimental work as Dr. Flexner is doing, for through study of the disease in animals it may, as he has emphasized, become possible to discover the way in which the virus is given off from infected individuals and the way it enters the bodies of the susceptible.

Reading in the library this week I noticed a report from Levaditi and Landsteiner which if verified ought to be of importance. These investigators assert that they have demonstrated the existence of the virus of acute anterior poliomyelitis in the salivary glands of the infected and they assume that the disease may be spread by way of the saliva. Dr. Flexner's ideas regarding the exit of the virus from the central nervous system by way of the naso-pharynx would fit in very well with Levaditi and Landsteiner's observations. One might think that the salivary glands become infected in this disease in the manner so often met with in bacterial infections of the salivary glands; namely, by way of extension from the buccal cavity along the salivary ducts. Though the suggestion has not been made, it seems to me easily conceivable that such salivary gland infection might explain the existence of virus-carriers for this disease. Just as after typhoid fever the gall bladder may long harbor living typhoid bacilli which, regularly or at intervals, are given off into the external world through the fæces, so it is easily thinkable that a certain number of individuals who have suffered from acute anterior poliomyelitis and have recovered therefrom may harbor the virus in the salivary glands and from time to time give it off through the saliva into the environment. Such carriers, should they be shown to exist, would help to explain the sporadic cases of poliomyelitis, the origin of which has hitherto been so puzzling. The idea of salivary infection is interesting also in connection with the apparent demonstration by Wickmann of contact infection in this disease.

The fact that the disease is due to a filterable virus, that its main expression is in the central nervous system and that the salivary glands become infected make its resemblance to rabies very close. Unfortunately experiments thus far made in preventive inoculation with dried spinal cords during the incubation period, have not been successful.

In the cases of acute anterior poliomyelitis which I have personally had the opportunity of observing the severe pains and stiffness of the limbs and neck at onset have been conspicuous features. These symptoms are probably due to meningeal involvement and a great deal more stress than formerly is laid now upon this feature of the disease. In a child I saw with Dr. Field, of Coburg, a few years ago the pains in the limbs and back were extremely severe and movement of the limbs caused so much pain that an acute articular rheumatism was thought of at the onset. A few days later the flaccid paralysis of both lower extremities and one arm unmasked the real nature of the disease.

Histological studies of the nervous tissues such as Dr. Flexner has demonstrated to us in lantern slides tonight are very instructive. They show how much more extensive the involvement of the whole nervous system is than one would suspect from the clinical symptoms observed. The disease process is not confined to the ventral horns at all but may involve all parts of the gray matter of the cord, the white matter, the meninges and the posterior root ganglia. More than this, the medulla oblongata, the pons, the basal ganglia and even the cerebral cortex show definite alterations of the same type as those met with in the cord itself. We can now begin to understand why it is that at times when anterior poliomyelitis is occurring in epidemic form, cases of acute disease of the central nervous system other than the typical flaccid paralyses due to anterior poliomyelitis are met with. Among these may be mentioned cases which simulate meningitis, others which simulate polyneuritis, others running the course of an acute ascending or descending spinal paralysis, others presenting the phenomena of bulbo-pontine palsies, others showing signs of a rapidly developing general ataxia and still others pursuing the course and presenting the phenomena of acute encephalitis with cerebral palsies of spastic type and with disturbances of intelligence. Only this autumn I saw here in town with Dr. Shearer a boy who two weeks after leaving a community in which acute anterior poliomyelitis had been epidemic suddenly developed acute symptoms which at first were very puzzling, but which we concluded were due to meningeal involvement and to lesions in the pons and medulla oblongata. There were no flaccid paralyses and the symptoms, though alarming for a time, gradually cleared up. Dr. von Pirquet also saw the case and will recall the difficulties of diagnosis.

This leads me to say a word regarding the nosological position of what we have been accustomed to call acute anterior poliomyelitis. It would seem, as those who have studied the northern epidemics especially have been led to believe, that acute anterior poliomyelitis is the most common expression, though not the only one, of a pathological process which involves more or less of the whole central nervous system. For some reason or another the cervical and lumbar enlargements of the spinal cord are most frequently and most severely involved in the pathological process, but higher parts of the nervous system may be concerned along with these and, in rare cases, without sufficient lesions in the cord to call forth flaccid paralyses. It has been suggested that the whole disease be called the "Heine-Medin disease" inasmuch as Heine and Medin gave the earlier important clinical descriptions. Dr. Flexner has already been able to produce experimentally in monkeys bulbar lesions sufficient to cause clinical paralyses and it will be interesting to find out whether or not all the forms of the Heine-Medin disease thus far observed, other than acute anterior poliomyelitis, may be produced in animals by experimental introduction of this same virus.

It is surprising how our classifications of disease become modified as soon as we get light regarding etiology. The etiology of acute diseases of the central nervous system has up to now been obscure and our classifications have depended almost wholly upon symptomatology rather than upon etiology.

Studies like these of anterior poliomyelitis promise to do for some of the nervous diseases what the discovery of the tubercle bacillus and its relations to various forms of tuberculosis has done in connection with pulmonary phthisis, scrofula, white swelling of joints, caries of bones, the serositides and lupus. It is becoming very clear that diseases of diverse parts of the nervous system presenting such different clinical phenomena that they have been described as wholly different diseases may be due to one and the same virus: thus each one of the eight or ten varieties of the Heine-Medin disease in human beings occurring in the same epidemic is probably due to one and the same virus, the different clinical picture depending upon the excessive localization of the pathological process in one or another part of the nervous system. Enthusiasts, however, should not run away with the idea that all acute processes in the central nervous system are due to the virus which causes epidemic poliomyelitis. That idea would be just as absurd as to assume that all of the infectious granulomata occurring in the body are due to the tubercle bacillus. Indeed, it seems now certain that acute infections of the meninges, acute myelitis acute encephalitis and even acute poliomyelitis may be due to different forms of infectious agents. I think it particularly interesting that Dr. Flexner has been able to study cases of poliomyelitis occurring spontaneously in the dog and in the chicken and to demonstrate that the virus obtained from the nervous system of these animals when injected into monkeys does not produce poliomyelitis in them. This would make it appear that poliomyelitis of the dog and of the chicken is due to some virus other than that which causes poliomyelitis in man and in monkeys.

As to the immunity conferred by one attack of acute anterior poliomyelitis in human beings, I may say that this immunity does not always develop quickly. While rare, relapses undoubtedly occur, and sometimes two or more relapses occur in the same individual, much as in typhoid fever. Whether or not there may be a second infection in later life with the same virus I do not know, though it is certain that persons who have suffered from acute anterior poliomyelitis leading to permanent paralysis of one lower extremity in childhood may in adult life develop a chronic anterior poliomyelitis or progressive muscular atrophy involving the other lower extremity. This phenomenon, however, is probably to be regarded as a late result of the first infection, the lower motor neurones having been so injured that they are unable later on to bear the strain of the wear and tear of life.

I would like to call attention to the great difficulty we sometimes experience in differentiating the Heine-Medin disease from acute multiple neuritis in children. It is rare to see cases of polyneuritis in children but they do occur and Dr. H. M. Thomas has made an especial study of them and has demonstrated them to us at this Society. Certain features are helpful in differentiation. The paralyses in multiple neuritis do not, as a rule, develop in their maximal distribution so abruptly as in poliomyelitis; usually at least several days or even weeks are required for the full development of the paralyses, in marked contrast with the non-progressive character of ordinary poliomyelitis. It must be borne in mind, however, and Foerster has recently emphasized this point, that occasionally in true anterior poliomyelitis the paralyses may progressively develop during a period of ten or twelve days. The pains in the muscles and nerves usually last longer in multiple neuritis than in poliomyelitis as does the fever, and sensory disturbances are much more common in neuritis, though in young children under three years of age this point is of little value for differential diagnosis since it is scarcely possible to make any adequate sensory analysis in patients so young. One differential point which I regard as of great significance, however, is the topography of the paralytic phenomena in the two diseases, especially in extremities in which only a portion of the muscles are involved. In multiple neuritis the paralyses correspond in topography to the distribution of the peripheral motor nerves, while in poliomyelitis the muscles involved are certain groups which are innervated by definite aggregations of nerve cells situated in the anterior horns of the spinal cord. Portions of different muscles concerned in the same synergistic activities become paralyzed in poliomyelitis so that the distribution here is wholly different from that corresponding to paralysis due to lesions of the peripheral motor nerves.

II. The Heart Muscle in Typhoid Fever. Dr. Louis Hamman.

The anatomical lesions produced by typhoid fever in the heart and blood vessels have long been known. While there is much diversity of opinion about the extent and frequency of these lesions their occurrence and importance is unquestioned. In our study of 43 hearts from patients dying of typhoid fever, we were able to find some changes in practically all, although in most the lesions were not extensive enough to allow one to assume with certainty that the efficiency of the heart muscle was compromised. There is unfortunately no satisfactory evidence at hand to allow us to judge the functional capacity of the heart by the character and extent of the histological lesions and frequently the two seem not to run parallel. In at least six of our cases both the fibre and interstitial lesions were so intense that we could hardly associate their presence with complete efficiency of the organ. We do not find any evidence of wide-spread change in the smaller branches of the coronary arteries but frequently periarteritis and endarteritis in the large medium-sized branches. No doubt these lesions must in some degree interfere with the blood nutrition of the heart and are of importance both for the immediate efficiency of the organ and its future integrity.

There are certain symptoms during the course of an acute infectious disease which point directly to the presence of some cardiac lesion and often to cardiac insufficiency, notably irregularities of rhythm, and the physical signs of beginning dilatation. Certain sudden deaths can be satisfactorily explained only upon the assumption of abrupt cardiac failure. Romberg has claimed that during the height of an infection the circulatory failure depends entirely upon vasomotor paralysis. Even though the vasomotor system plays the important rôle the work of Stejskal shows that the heart is not always perfectly efficient and that it cannot be entirely disregarded as a

factor in the failure. It is during convalescence particularly that the symptoms of a damaged myocardium stand out most clearly. Such symptoms are not nearly so common after typhoid as after other infections, notably diphtheria, but they occur frequently enough to indicate the significance of the damage the heart has sustained.

Undoubtedly these lesions of the myocardium and of the arteries, principally the coronaries, are of the greatest importance for the future health of the individuals. We are being more and more impressed with the significance of infectious diseases in the production of chronic arterial and myocardial disease. Typhoid fever has not in this regard the same importance as rheumatism, syphilis, or diphtheria, but on account of its prevalence, it is a factor to be seriously reckoned with. The prevention of infectious diseases will probably prove one of the strongest prophylactic measures against the degenerative lesions of the circulatory system.

Discussion.

Dr. Hirschfelder.—In death from circulatory failure in infectious disease there is often no parallelism between the intensity of the demonstrable lesions and the failure of the circulation. The areas of infiltration and vacuolization in the heart muscle, mentioned by Dr. Hamman are in themselves too small to cause such great functional disturbance; and yet the failure of the circulation is due in great part to failure of the heart itself. Another cause must be sought for this. It is a failure of the heart muscle as a whole. There is a lowering of the tonicity of the heart muscle. It is the lowering of the tonus which distinguishes the diseased heart muscle from the healthy. This point is particularly well shown in phosphorus poisoning, a condition in which, as Dr. Hamman has pointed out, degeneration and the vacuolization of the fibres occur as they do in typhoid fever. De la Camp has found that if he caused dogs poisoned with phosphorus to run on a treadmill, their hearts became dilated from exercise which did not affect the size of the normal hearts at all, or if anything caused them to become smaller. Nevertheless there is often no change in blood pressure. Kraus also has called attention to similar observations in man, the dilatation occurring even when the blood pressure and cardiac outline before the effort were perfectly normal. The diminished tonicity of the heart muscle enables more blood to enter the heart during diastole, though the unchanged or diminished strength of the beat enables the heart to drive out only its usual quota of blood (systolic output). Dilatation therefore sets in through increase of the "residual blood." Any severe strain will tend to overfill a heart whose tonicity is much diminished, even to the point at which it can no longer carry out effectual contractions, and may thus bring about the death of the animal patient.

I should like to ask Dr. Hamman whether any difference has been found between the heart lesions in patients who had been given a liberal diet and those who had been given only milk and albumen during their illness. Schieffer has shown that a definite atrophy of the heart may occur from inanition alone; and since it is a well-known principle in pathology that the effect of two deleterious agents acting simultaneously is more intense than if they were acting at different times, it would be of interest to know whether the insufficient diet loss of body proteid which occurs upon a milk and albumen diet may not in itself act as a contributing factor which renders the increasing severity of the heart lesions due to typhoid fever. This is a question of particular importance since it has been shown by Dr. Voegtlin in this clinic, by Dr. Shaffer in New York, and by numerous European observers that much of the proteid loss of body proteid can be obviated by a diet rich in carbohydrates; and since clinical experience has shown that during convalescence, when the chief strain falls upon the circulatory system, the patients who have been upon a liberal diet are usually the stronger, and that the period required for convalescence has been shortened to about half what it was during the days of the restricted diet treatment.

III. Anerythraemic Erythraemia. Dr. Roger S. Morris.

This paper appeared in the Bulletin for February, 1910.

THE LAENNEC.

January 24, 1910.

Dr. Henry Barton Jacobs in the chair.

I. The Visiting Nurse's Attitude Towards Certain Tuberculosis Problems. Miss Ellen La Motte.

See current number.

II. Relative Importance of the Human and Bovine Types of Tubercle Bacillus in Human Tuberculosis. Dr. W. H. Park.

The investigations under Dr. Park's supervision have been directed towards the study of the frequency of occurrence of the bovine type of the tubercle bacillus, amongst the cases of tuberculosis, coming under his attention in the New York Health Department and in certain hospitals.

These investigations, by a number of workers in the Department laboratories, have been carried on over a period of two and a half years and are not yet fully completed. Dr. Charles Krumwiede, Jr., has had charge of the details of the work. That human beings may be infected with the bovine type of the tubercle bacillus has long been recognized. The source of the infection being usually milk and butter from tuberculous cattle. A very satisfactory differentiation of the two types—bovine and human—tubercle bacilli can be made on the egg and glycerine-egg media. The human type growing very much more luxuriantly in the early generations on the egg media. The addition of glycerine increases this difference as in most cases it inhibits the bovine culture and stimulates the growth of the human cultures.

The different schools vary in their idea of the permanence of the two species, many believing that one type may later assume the characteristics of the other type. The bovine type is thought by these persons to lead to more infections than the study of cultures would indicate since they believe many individuals are infected during infancy with the bovine type,

which later, changes over to the human type. That this or the reverse change is possible is suggested by the results of the recent British Commission, in an experiment in which several cultures of the human type of the bacillus were passed through calves, during which process the type of the bacillus was apparently changed to that of the bovine type. In other instances no change took place. It is considered by many that the apparent change in type was simply due to accidental infection of the calves with bovine bacilli.

In all of Dr. Park's experiments in calves the human type remained the human type throughout, and there was no tendency to change over to the bovine type. Furthermore, the bovine type was just as characteristic in the lymph glands, in which infection had existed for one or two years, as in the freshly infected cases. In 412 cases of tuberculosis, carefully studied, clinically and from portions of glands and tissue removed at operation or at autopsy, Dr. Park has found the relative occurrence of the two types of bacilli as follows:

412 Cases of Tuberculosis.

Diagnosis. Type.	Adults. 16 years over. H.	Children 5-16 years. H.	B.	Under 5 years. H.	B.
Pulmonary	277	8	..	5	..
Cervical adenitis	9	19	7	5	11
Generalized	2	1	..	13	5
Generalized with meningitis	..	1	..	31	1
Bones and joints	1	10	..	6	..

It is interesting and important that the occurrence of the bovine type is practically limited to the cases under 16 years of age and with the larger proportion under five years of age. Above the age of 16 years the human type is practically the only type found.

In the study of 40 cases taken from the Babies' Hospital, New York City, Dr. Park finds over 10 per cent of the infections due to the bovine type of the bacilli, and he believes that his figures will show that, in general over 3 per cent of all the cases of tuberculosis are due to the bovine type. Dr. Park agrees with Dr. Koch, that as far as adults are concerned, the bovine type of the bacillus may be considered a negligible factor.

In the ordinary case of pulmonary tuberculosis we have not to deal with the bovine bacillus.

In infants and young children, however, bovine infection causes many deaths and deserves that we give serious consideration to its prevention. This can best be done by safeguarding the milk and butter supply of young children.

Discussion.

Dr. William Welch.—It is interesting to consider our knowledge of the bovine type of the bacillus, before Prof. Koch made his famous statements at the recent London Congress. For many years it was believed that there was no difference between the two types and it is true that this view is held by some even to the present day.

Dr. Park's investigations are most important and will when completed represent an infinite amount of time and painstaking work. His cases were not picked cases since they included also all the cases of ordinary tuberculosis, and therefore the statistics and results of his work will prove most valuable. It is suggestive that the infection in tuberculous meningitis is from other than an alimentary source since the bovine type of the bacillus is so rarely found.

NOTES ON NEW BOOKS.

Tuberculosis of the Nose and Throat. By Lorenzo B. Lockard, M. D., Laryngologist to the Jewish Consumptive Relief Society Sanatorium, etc. (*St. Louis: C. V. Mosby Company, 1909.*)

Dr. Lockard's work presents in good form the most exhaustive American treatise on tuberculosis of the upper air passages. After a short historical survey of the lesions of the various organs concerned, he presents in detail the symptoms, signs and treatment of the lesions in the larynx, nose and pharynx. He emphasizes the fact that the prognosis in this disease is not, as too frequently thought, hopeless. If recognized early, a great many of the cases can be cured or the process arrested.

The volume is well made up and will be a most valuable addition to the laryngologist's library.

Sylvan Rosenheim.

Modern Clinical Medicine: Diseases of Children. Edited by Abraham Jacobi, M. D., LL. D., etc. An authorized translation from "Die Deutsche Klinik" under the general editorial supervision of Julius L. Salinger, M. D. Illustrated. (*New York and London: D. Appleton & Co., 1910.*)

He must be a valiant critic who takes issue with the leader of American pædiatrists, the editor of this work, the greatly revered and respected Dr. Jacobi. In spite of the latter's enthusiasm for the book, it seems to the reviewer to have certain distinct limitations. In his preface Dr. Jacobi says: "The articles contained in it are all written by masters of national or international renown, are evidently weighed with care and circumspection, guided by learning, convey everything that is worth possessing, are complete but brief, brief but lucid, lucid and in part eloquent and easy reading. No extensive editing could have enhanced their value. As, moreover, the admirable translation by Dr. J. L. Salinger has provided a book at least as readable as the original, I recommend it to the attention of the professional public as a worthy and valuable addition to their libraries." (With such praise the publishers should have been satisfied and not asked for more or run the risk of having their work found fault with!) It is not our intention to be hypercritical, but a little over a page for "cerebrospinal meningitis" does not seem to deserve such words as those of the editor. In this unsatisfactory account of the disease there is no mention of any form of serum treatment. In the chapter on scarlet fever under "Prophylaxis and Treatment" it is stated "that, naturally, there should be a disinfection of all utensils and objects which have come into contact with the patient. . . . . It is impossible to enter here more minutely into these hygienic questions." Such cursory treatment of an important question in a text-book which is assumed to be first-class is not excusable. What notes the editor has added have enhanced the value of the book for American readers, and it is a pity that

there are not more of them. The work is too distinctly German to be appreciated by the average student or physician, for there is very little note taken of the work done by any one outside of Germany. To this fact the editor calls attention in his preface, and while we agree with him in thinking that such an exposition of German views is valuable, yet, except to the thorough student of pædiatrics, it does lessen the worth of the book to the average reader. The translation, lauded by the editor, is good, but due to the translator's desire "to adhere as closely as possible to the style and phraseology of the German authors," it is frequently not easy reading. It is practically impossible to render into fluent English the involved German phraseology, and it is not worth while to make the attempt, for German and English style in prose writing are too distinctly different to be harmonized. The few illustrations do not add merit to the book, but the charts are excellent. In spite of these reflections the book is a most valuable one for the advanced student of pædiatrics, who in comparatively small compass will find here the views of the leading German authorities in this science.

Fiske Fund Prize Dissertation. The Mode of Infection and Duration of the Infectious Period in Scarlet Fever. By Charles V. Chapin, M. D., Providence, R. I. (*Providence: Snow & Farnham Company, 1909.*)

The author has presented in his essay briefly and clearly the latest views on this subject, and the paper is one well worth careful reading. Infection is being observed from so many different points of view that theories held to-day may be upset to-morrow, and certainly until the cause of a fever is known, any theory as to its method of infection must be debatable. Dr. Chapin from his studies draws these, among other conclusions, that scarlet fever is most contagious during the first days of its appearance, that it is probably a local disease of the nose and throat and that the exfoliated epidermis is probably not infectious—all points of great interest, which, however, require further study before they can be accepted as proven.

Bacteriology for Nurses. By Isabel McIsaac. Price $1.25. (*New York: The Macmillan Company, 1909.*)

The authoress has written several works on nursing, and has acquired a too easy faculty of preparing handbooks of one sort or another. Her last work cannot be commended. It is not well composed. The chapter on tuberculosis, for example, might well have been written by a high school pupil; and there are throughout the book paragraphs which need emendation.

Treasury Department. Public Health and Marine Hospital Service of the United States. Hygienic Laboratory. Bulletin No. 52, October, 1909. Report No. 3 on the Origin and Prevalence of Typhoid Fever in the District of Columbia (1908). By M. J. Rosenau, L. L. Lunsden and Joseph H. Kastle. (*Washington: Government Printing Office, 1909.*)

Those who have read the first two reports on this subject by these authors will be anxious to read this third excellent and exhaustive one. It is doubtful whether there is any such thorough study of the fever in a community. The conclusions of the writers who have so painstakingly examined into all the conditions surrounding the prevalence of typhoid fever in Washington (D. C.) deserve the greatest respect and consideration by all students in hygiene. They state that "the results of three years of study show that the disinfection of excreta of patients is frequently inefficient or neglected, and that there is need of legal control of typhoid fever patients, and typhoid bacillus carriers." "We are convinced that a vigorous campaign against typhoid fever as a 'contagious' disease, and the adoption of measures that would prevent the spread of the infection in milk, would eliminate the greater part of typhoid fever from the District of Columbia."

Diet in Tuberculosis, with Costs of Foods and Their Preparation. By Noel Dean Bardswell, M. D., M. R. C. P., and John Ellis Chapman, M. R. C. S., L. R. C. P. Price $1.00. (*Oxford University Press, American Branch, 35 West 32d Street, New York, 1910.*)

This pamphlet contains in a brief and practical form the results of investigations previously published, somewhat more extensively, in a volume entitled "Diets in Tuberculosis," which was reviewed in the Johns Hopkins Hospital Bulletin for June, 1908. In this pamphlet are added many directions for the proper preparation of foods. It is a valuable and helpful treatise on the subject.

A Text-book upon the Pathogenic Bacteria. For Students of Medicine and Physicians. By Joseph McFarland, M. D., Professor of Pathology and Bacteriology in the Medico-Chirurgical College, Philadelphia. Sixth Revised Edition. Illustrated. Price, $3.50. (*Philadelphia and London: W. B. Saunders Company, 1909.*)

The new edition of McFarland's Text-book upon the Pathogenic Bacteria presents but few points of difference between it and previous editions, upon which we have already had occasion to comment favorably. The book contains a vast amount of valuable information and the treatment of the majority of the topics is adequate. Mixed with this information, however, there is much that is erroneous, and many statements are made that are apt to lead the student far astray. In the chapter on Yellow Fever, to quote specific instances, over seven pages are devoted to the consideration of Bacillus X of Sternberg, Bacillus icteroides of Sanarelli, and the Bacillus of Havelburg. At no time was there any satisfactory evidence that these organisms were etiologically related to yellow fever, and with our present knowledge a detailed description of their properties is quite out of place in a chapter devoted to this disease. The most important work on yellow fever, the investigations of the American Commission, is dismissed with a scant three pages.

Much the same criticism may be expressed in regard to the chapter on Hog Cholera. The hog cholera bacillus is now admitted to have no definite etiological relationship to hog cholera, although it may play the rôle of a secondary invader. Uhlenhuth has shown, however, that this bacillus is not the only one to play this rôle in this disease, even Bacillus coli apparently being able to assume this function. Nearly 10 pages are devoted to this microorganism. None of the great advances in our knowledge of hog cholera begun by DeSchweinitz, worked out by Dorset, McBride and Bolton, and now confirmed by a number of investigators in Germany, France and Holland, are adequately presented, although the causation of this disease by an ultra-microscopic virus, and not by the hog cholera bacillus, is now almost universally accepted. At the same time little is said of the exceedingly interesting subject of the immunity of this disease, and the methods of vaccination adopted both abroad and in this country, in which thousands of swine are inoculated first with immune blood, then with virulent blood, or after inoculation with immune blood, are exposed to natural infection, are not even mentioned.

Surely in a text-book of bacteriology, published in America and written by an American, two of the most original and valuable pieces of investigation ever accomplished by American investigators should receive more extensive and more favorable comment than Dr. McFarland has accorded them.

It might also be stated that the bacillus described by Bordet and Gengou in pertussis, the presence of which in whooping-cough cannot be doubted, is apparently not mentioned.

In general we believe this book needs thorough revision, the elimination of many unimportant pages, and the incorporation of some of our recently acquired knowledge, in order that it can be recommended to students of bacteriology.

Diseases of the Stomach. A Manual for Practitioners and Students. By S. H. Habershon, M. A., M. D., F. R. C. P. Illustrated. Price, $2.50. (*Chicago: Chicago Medical Book Company, 1909.*)

We may say at once that the author of this work deserves our thanks for having written a work on gastric disorders without giving us a new classification and without coining new terms. Formerly nearly every writer on the subject thought it his duty to do both, but fortunately this tendency seems to have become less marked of late, for which we have cause to be grateful. The work opens with an excellent chapter on the anatomy of the stomach in which are some very good plates. Following this the writer takes up the subject of the physiology of the digestion and the importance of a thorough knowledge of this in handling the diseases of the digestive tract is only too evident. After this are chapters on diet and the methods of examination. In the discussion of the general symptoms of gastric disease it seems at times that the author has gone rather far afield and brought in other diseases. A large section is devoted to the discussion of dyspepsia, of which term the writer does not give an exact definition, but apparently uses it in a general way to characterize disturbances of the digestive function which perhaps cannot be easily classed anywhere. Certainly the term is a convenient one and, as the writer says, an exact classification is extremely difficult.

It is not possible to follow up every section in detail, but it may be said that the discussion throughout is to be thoroughly commended on the whole. There is thorough attention given to the subject of diet and to the employment of general measures. There are, however, two or three points which seem worthy of criticism. Thus, anorexia nervosa is discussed under the general heading of dyspepsia and under the subdivision of nervous dyspepsia of central origin. It seems a mistake to regard this disease as one of the digestive system. It is better considered as a severe general neurosis. The author notes that death has occurred and states that this could only happen in neglected cases. This is hardly correct, as the experience of this clinic has shown. A point which is open to criticism is the discussion of the diagnosis between cancer of the stomach and pernicious anæmia. The writer states that in the absence of a tumor the difficulties of diagnosis are increased by the character of the blood. This does not seem a correct statement as in doubtful cases it is to the study of the blood that we must turn to give the diagnosis. There is a rare case in which the diagnosis may be in doubt for a time, but this does not happen often. It is also rather surprising to find a man from London speaking of progressive pernicious anæmia as being originally described by Biermer. We were of the opinion that this honor belonged to Addison. A point which might be amended is the mention of the absence of digestive leucocytosis as a diagnostic sign of cancer of the stomach. This is mentioned with reference to an article written in the year 1894. It would have been better to have brought this subject up to date, because experience has shown that the absence of digestive leucocytosis is of little value as a diagnostic sign.

Altogether, however, we must say that Dr. Habershon has given us an excellent work and one which should be of much help to the student and practitioner. The directions for treatment are clear and satisfactory, while in the whole discussion the author has kept clear of fads and fancies, which many would say is as admirable as it is rare in a writer on digestive disorders.

Medical Chemistry and Toxicology. By James W. Holland, A. M., M. D. Second edition, revised and enlarged. (*Philadelphia: W. B. Saunders Company, 1908.*)

The author has crowded an immense amount of information into this volume, but has not succeeded in giving a deep, thorough and comprehensive treatment of either medical chemistry or toxicology. The book deals with all branches of chemistry of interest to the physician, but so lacks in detail that the desire to consult other sources of information is constantly arising. Unfortunately no bibliography is attached, so that the reader is often left without access to the details which he is seeking.

The section dealing with standardization of normal solutions is very vague and is not comprehensive enough for working directions for the ordinary medical student.

Too little attention has been paid to exact quantitative methods of estimation; for example, no quantitative method of estimation of creatinin or ammonia is given, while the Kjeldahl method described is crude and cumbersome when compared with such a method as that adopted by the Bureau of Chemistry, U. S. Department of Agriculture.

The space allotted to autolytic enzymes is entirely too small. Certain ferments are ascribed to certain organs, no mention being made of the species and no account taken of the difference in the distribution of these ferments in different species of animals.

The toxicology of the metals is satisfactory, generally speaking, but that of the organic vegetable preparations constantly employed by the physician has been very much neglected in parts—for instance, no toxicology at all is given of digitalis, strophanthus, ergot, and many other important drugs.

An attempt has been made to crowd too much into too small space with the result of a too superficial treatment of some subjects, while some other subjects worthy of consideration in such a book have been absolutely ignored. L. G. R.

Practical Diatetics, with Special Reference to Diet in Diseases. By W. Gilman Thompson, M. D., etc. Fourth edition. Illustrated, enlarged and completely rewritten. Price, $5.00. (*New York and London: D. Appleton & Co., 1909.*)

Since the first edition of Practical Diatetics was published the treatment of disease by diet has come to hold a place of first importance. During the fifteen years which have elapsed much scientific investigation has been made.

In the present edition, while the classification of food is much the same as in the early one, many unimportant details have been eliminated, while in some cases sentences have been rewritten with a view to simplicity and better arrangement of information. Tables have been omitted which recent scientific investigations have proved inaccurate, and in estimating the equivalent elements in the different classes of food many changes have been made and new figures adopted in making the various food computations.

The results of the various recent investigations and experiments showing the difference in the body requirement at rest and at work, as determined by the measurement of the intake of air, food and water and output of oxygen, carbon dioxide and water, by Benedict and Milner, are inserted.

Many experiments showing metabolic changes have been added and the newest methods which are employed to study the energy-producing power of food in the body. A distinction is made in the use of the terms protein and proteid.

A detailed account of the experiments made through the Atwater and Rosa calorimeter at Wesleyan University with the results obtained is given in this edition. Instead of old authorities present-day investigators are quoted, such as Atwater, Sherman and Waite.

The use of chemical food preservatives has increased so much of late years as to require restriction by legislation. Dr. Wiley has made many exhaustive studies and a summary of his experiments on what was known as "The Poison Squad," published in several bulletins authorized by the Department of Agriculture, is given here. The result of the investigation, which excited so much comment that a special commission was appointed by the National Government to report upon it, signed by Professors Chittenden, Remsen, Long and Herter, is likewise published in

this volume together with another investigation by Professors Chittenden and Gies on the same subject. A report on the work of the French Commission of Public Hygiene has been added.

Laws with reference to the marketing of milk which have been enacted since the time of writing the first book are here summarized together with the methods employed by the various milk commissions formed for the purpose of supervising the transportation and production of milk so as to ensure its purity.

Plates are added showing different pieces of apparatus by which many of the modern milk tests have been made and those used for other experimental purposes in connection with model milk laboratories.

Many new ideas with reference to treatment in disease by diet are given a place in this volume. Dr. Irving Fisher of Yale is quoted with reference to food absorption, good equivalents and good portions, and the new idea of feeding in typhoid fever, as outlined by Coleman-Shaffer, has been added. Altogether the book has been rewritten so as to make it authoritative and in every way a present-day work, eliminating all the older ideas which recent experiments have proved to be valueless.

BOOKS RECEIVED.

A Textbook of Experimental Physiology. By N. H. Alcock, M. D., D. Sc., and F. O'B. Ellison, M. D. With a preface by E. H. Starling, M. D., F. R. C. P., F. R. S. 1909. 8vo. 139 pages. P. Blakiston's Son & Co., Philadelphia.

Transactions of the Association of American Physicians. Twenty-fourth session held at Washington, D. C., May 11 and 12, 1909. Volume 24. 8vo. 634 pages. Printed for the Association, Philadelphia.

Oxford Medical Publications. Diseases of the Heart. By James Mackenzie. Second edition. 1910. 8vo. 419 pages. Oxford University Press, American Branch, New York.

Ophthalmic Surgery. A Treatise on Surgical Operations Pertaining to the Eye and its Appendages, with Chapters on Para-Operative Technic and Management of Instruments. By Charles H. Beard, M. D. With 9 plates, showing 100 instruments and 300 other illustrations. 1910. 8vo. 674 pages. P. Blakiston's Son & Co., Philadelphia.

Spondylotherapy. Spinal Concussion and the Application of Other Methods to the Spine in the Treatment of Disease. By Albert Abrams, A. M., M. D. (University of Heidelberg), F. R. M. S. Illustrated. 1910. 8vo. 400 pages. Philopolis Press, San Francisco, California.

Urgent Surgery. By Félix Lejars. Translated from the sixth French edition by William S. Dickie, F. R. C. S. With 20 full-page plates and 994 illustrations, of which 602 are drawn by Dr. E. Daleine and A. Leuba, and 217 are from original photographs. Vol. 1. Introductory—Head—Neck—Chest—Spine—Abdomen. 1910. 4to. 617 pages. William Wood & Co., New York.

Oxford Medical Publications. Male Diseases in General Practice. An Introduction to Andrology. By Edred M. Corner, M. A., M. C. (Cantab.), B. Sc. (Lond.), F. R. C. S. (Eng.). 1910. 8°. 462 pages. Oxford University Press, American Branch, New York.

Oxford Medical Publications. Constipations and Allied Intestinal Disorders. By Arthur F. Hertz, M. A., M. D. Oxon., M. R. C. P. 1909. 8°. 344 pages. Oxford University Press, American Branch, New York.

Oxford Medical Publications. Diet in Tuberculosis, with Costs of Foods and Their Preparation. By Noel Dean Bardswell, M. D., M. R. C. P., and John Ellis Chapman, M. R. C. S., L. R. C. P. 1910. 8vo. 62 pages. Oxford University Press, American Branch, New York.

A Textbook of Nervous Diseases. By William Aldren Turner, M. D. (Edin.), and Thomas Grainger Stewart, M. B. (Edin.). 1910. 8vo. 607 pages. P. Blakiston's Son & Co., Philadelphia.

The Stomach, Intestines and Pancreas. By W. C. Bosanquet, M. A., M. D. Oxon., F. R. C. P., and H. S. Clogg, M. S. (Lond.), F. R. C. S. (Eng.). Edited by James Cantlie, M. A., M. B., C. M. (Aberd.), F. R. C. S. (Eng.). The Medico-Chirurgical Series No. 2. 1910. 12mo. 665 pages. William Wood & Co., New York.

Diagnostic Therapeutics. A Guide for Practitioners in Diagnosis by Aid of Drugs and Methods Other than Drug-Giving. By Albert Abrams, A. M., M. D. (Heidelberg). With 198 illustrations. [1910.] 8vo. 1039 pages. Rebman Company, New York.

Living Anatomy and Pathology. The Diagnosis of Diseases in Early Life by the Roentgen Method. By Thomas Morgan Rotch, M. D. 303 illustrations. [1910.] 8vo. 225 pages. J. B. Lippincott Company, Philadelphia and London.

Diseases of the Genito-Urinary Organs. Considered from a Medical and Surgical Standpoint, including a description of Gonorrhea in the Female and Conditions Peculiar to the Female Urinary Organs. By Edward L. Keyes, Jr., M. D., Ph. D. With 195 illustrations in the text, and 7 plates, 4 of which are colored. 1910. 8vo. 975 pages. D. Appleton & Co., New York and London.

Nutrition and Dietetics. A Manual for Students, for Trained Nurses, and for Dietitians in Hospitals and Other Institutions. By Winfield S. Hall, Ph. D., M. D. 1910. 8vo. 315 pages. D. Appleton & Co., New York and London.

Preparatory and After-Treatment in Operative Cases. By Herman A. Haubold, M. D. 1910. 8vo. 650 pages. D. Appleton & Co., New York and London.

Manual of Operative Surgery. By John Fairbairn Binnie, A. M., C. M. (Aberdeen). Vol. II. Vascular System, Bones and Joints, Amputations. Fourth edition, revised and enlarged. With 550 illustrations. 1910. 12mo. 553 pages. P. Blakiston's Son & Co., Philadelphia.

Serum Diagnosis of Syphilis and the Butyric Acid Test for Syphilis. By Hideyo Noguchi, M. D., M. Sc. 14 illustrations. 1910. 8vo. 173 pages. J. B. Lippincott Company, Philadelphia and London.

Guy's Hospital Reports. Edited by F. J. Steward, M. S., and Herbert French, M. D. Vol. LXIII, being Vol. XLVIII of the third series. 1909. 8vo. XXXVI + 385 pages. J. & A. Churchill, London.

An English Handbook to the Paris Medical School. By A. A. Warden, M. D. Second edition. (With map.) 16mo. 52 pages. J. & A. Churchill, London. P. Blakiston's Son & Co., Philadelphia.

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CONTENTS.

EXPERIMENTAL HYPOPHYSECTOMY.[1]

By S. J. Crowe, M. D., Harvey Cushing, M. D., and John Homans, M. D.

(From the Hunterian Laboratory of Experimental Medicine, The Johns Hopkins University.)

SUBJECT HEADINGS.

I. Introduction.

The function of one of the so-called ductless glands may be investigated by two principal methods. These may be designated as the positive and the negative methods of studying glandular physiology. The first embraces such procedures as the introduction of the gland or its extracts into the body by feeding or injection in order to produce reactions comparable to those which would be brought about by an exaggeration of the normal glandular activity. By the negative method observations are made upon the effects of lost or diminished function of the gland brought about by its complete or partial experimental removal—conditions therefore simulating grades of hypoactivity.

In the course of our work on the function of the hypophysis many experiments have been made by both of these methods, but the particular object of this paper is to record the results obtained by the indirect or negative method, which should enable us to determine:

(1) Whether the hypophysis, in whole or in part, is necessary for the maintenance of life.

(2) If essential, what symptoms occur antecedent to death.

(3) If not essential to life what effects, if any, are produced by its removal.

(4) Whether after partial removal of the gland definite symptoms supervene in consequence of diminished secretion, and whether a compensatory hypertrophy may occur.

(5) Finally, which of the anatomical subdivisions of the gland is chiefly responsible for the symptoms, if any, which follow the loss or mutilation of the structure as a whole.

In order to secure uncomplicated and trustworthy results by this indirect method of investigating glandular function it is

[1] Certain aspects of our investigations dealing with specific questions have already been published (Effects of Hypophyseal Transplantation Following Total Hypophysectomy in the Canine. *Quart. J. Exper. Physiol.*, 1909, II, No. 4, 389; The Experimental Production of Adipositas Universalis with General Atrophy (Hypopituitarism) to appear in Ziegler's Beiträge) and one of us (Cushing) has advanced some general views on the subject in an attempt to correlate the experimental findings with the clinical phenomena associated with various hypophyseal lesions (The Hypophysis Cerebri: Clinical Aspects of Hyperpituitarism and of Hypopituitarism. *J. Am. M. Ass.*, 1909, LIII, 249. Partial Hypophysectomy for Acromegaly, with Remarks on the Function of the Hypophysis. *Ann. of Surg*,. 1909, L, 1003. The Function of the Pituitary Body. *Am. J. M. Sc.*, 1910, CXXXIX, 473). It is anticipated that further papers dealing with the circulation of the hypophysis, the histologic appearance of the gland associated with varying grades of activity, the alterations of other ductless glands secondary to hypophysectomy, the effects of injection of extract in states of hypopituitarism, and a special discussion of the symptoms of polyuria, glycosuria, etc., will subsequently appear.

necessary, in the first place, that some procedure be devised by which the structure can be approached and manipulated with reasonable assurance of making a clean-cut lesion without complication from hæmorrhage, infection or from such injury of adjoining structures as might confuse the subsequent symptomatology. It is here that the introduction of modern surgical methods in experimental physiology plays its chief rôle, particularly in the case of structures as difficult of access as is the pituitary body. In the second place, past experience has shown that it is absolutely essential to make a thorough post-mortem microscopic study of the infundibular region, for naked-eye appearances do not justify one in passing judgment upon the totality of removal.

In order to fully interpret the confusing results of past experimentation, it is necessary to bear constantly in mind these two important factors, for one or the other of them has usually been wanting.

II. Historical Review.

Reports have been made upon the effect of experimental hypophysectomy carried out on a variety of creatures—frogs, tortoises, chickens, guinea-pigs, rabbits, cats and dogs. In the attempt to find a satisfactory surgical route to the gland in one or another of these species, numerous procedures have been advocated. These may be subdivided into extracranial and intracranial methods of approach to the sella turcica. By the *extracranial* method the gland has been approached from below in the mid-line through the nasal, buccal, hyoid and pharyngeal regions, or from below and to one side by a lateral pharyngeal and spheno-palatine route. By the *intracranial* procedure it has been approached from above through a median opening in the cranial vault, or from the side by an opening in the temporal region with elevation of the subjacent lobe. Mere statements of their performance are all that we possess of the earlier experiments. Thus in a discussion of the paper by Tiedeman and Mass in 1900, Koenig[2] states that Julius v. Michel in 1881 attempted, by a frontal approach, to remove the gland from a number of dogs, cats and rabbits. Most of the animals were lost owing to immediate operative complications, but some survived for long periods.

Sir Victor Horsley was apparently the first to publish a personal note regarding the experimental removal of the gland. In an article [3] dealing largely with the functions of the thyroid a brief statement is made to the effect that he had removed the pituitary body from 2 dogs, which were sacrificed at the end of 5 and 6 months, respectively, and that the hypophysectomy led to no disturbing symptoms. No details are given beyond the fact that the motor cortex was found to be exceptionally excitable in both animals. This casual statement doubtless was given wider circulation than its distinguished author anticipated.

The first actual contribution to the subject was made in 1892 by Marienesco,[4] who had been associated with Marie in the earlier study of acromegaly. In his brief article he mentions (without reference) some experiments of Dastre's undertaken 3 years previously, in which the gland was approached through the mouth: the animals all succumbed. Marienesco's operations, also conducted by the buccal route, were made upon 8 cats. In his procedure the soft palate was divided, the base of the skull under the sella turcica was trephined and the hypophysis, so far as possible, destroyed with a cautery. Three of these 8 animals survived the operation and lived, respectively, 3, 5 and 18 days. In the interim they lost flesh rapidly in spite of forced feeding, and acquired a subnormal temperature. There was no post-mortem evidence of infection or hæmorrhage: the hypophysis on gross examination was absent, but there was no microscopical confirmation of the apparent complete destruction of the gland. Marienesco concluded that loss of the gland is compatible with life for some weeks.

Gley, whose important contributions to our knowledge of the cervical glands are well known, in 1892 reported a single experiment on the hypophysis of a thyroidectomized rabbit.[5] Through a trephine opening in the mid-cranial vault an instrument was introduced through the cerebrum into the sella turcica and an attempt made to destroy the gland in this blind fashion, with most unsatisfactory and inconclusive results.

The first studies which include any suggestive observations on the symptomatology of apituitarism were published in 1892 and 1894 by Vassale and Sacchi.[6] By an operative approach differing only in a few minor details from that employed by Marienesco an attempt was made to destroy the gland by the use of the thermo-cautery and chromic acid. All but 18 of the 23 dogs and 17 cats that were used succumbed to operative complications of hæmorrhage or infection. Of the animals which escaped these complications the greater number died during the first week, the longest survival being 14 days, and it was found that the gland in this animal had not been entirely destroyed. The total removal of the gland, therefore, regardless of operative complications, was regarded as necessarily fatal.

Their later report included a description of the 1 dog which had survived a supposedly complete removal for 37 days and another a partial removal for over a year. In the latter case a fragment of anterior lobe was obviously present, but no microscopic examination of the base of the brain seems to have been made in the cases in which naked-eye appearances made it seem probable that the extirpation had been complete.

The symptoms which were observed in the fatal cases were psychic depression, apathy, motor disturbances in the shape of fibrillary and irregular muscular movements, lowering of temperature, polydipsia, anorexia, loss of weight and ultimate

[2] *Berl. klin. Wchnschr.*, 1900, XXXVII, 1040.

[3] Functional nervous disorders due to loss of thyroid gland and pituitary body. Abstract of third Brown Lecture. *Lancet*, 1886, I, 5.

[4] M. G. Marienesco: De la destruction de la glande pituitaire chez le chat. *Compt. rend. Soc. de Biol.*, 1892, IV, N. S. 509-510.

[5] E. Gley: Recherches sur la function de la glande thyroide. *Arch. de physiol. norm. et path.*, 1892, IV, 311-326.

[6] Sulla distruzione della ghiandola pituitaria. *Riv. sper. di Freniat. Reggio-Emilia*, 1892, XVIII, 525-561.

Ulteriori esperienze sulla ghiandola pituitaria. *Ibid.*, 1894, XX, 83-88. Also Atti d. XI Cong. med. internaz. Roma, 1904. *Il Patol. gen.*, 163-165.

coma; less constant symptoms were rigidity of the hind-legs, curvation of the spine, convulsions, vomiting and polyuria. The authors concluded that the hypophysis was of great physiological importance; that its loss was incompatible with life and that, like the thyroid, it produced a secretion, in the absence of which a fatal autointoxication might occur.

Gatta, in 1896,[7] by a buccal procedure similar to that employed by Vassale and Sacchi, attempted to destroy the hypophysis in 4 cats after a primary thyroidectomy. Death occurred in from 8 to 18 days, preceded by a failure of general nutrition and lowering of temperature, albuminuria and rigidity of the hind-legs. There was no microscopical control, but the author concluded that the hypophysis was essential to the maintenance of life.

In the following year (1897), after some similarly incomplete experiments carried out by the buccal route with an additional temporary tracheotomy, Biedl[8] reached the opposite conclusion, namely, that the gland is not vitally important. Pineles[9] makes brief mention, likewise, of a number of attempted buccal extirpations on cats undertaken in the Physiological Institute in Vienna, in which the results were entirely negative, as only 2 of the animals survived, and a subsequent examination showed that the removal had been incomplete.

At this time Cyon, in a series of articles in Pflüger's Archives (1898-1900),[10] advanced his well known views in regard to the supposed function of the hypophysis in regulating intracranial blood pressure. In the course of these experiments he exposed the gland and stimulated it (mechanically and electrically), and thought that he obtained results similar to those produced by vagal stimulation, whereas its total destruction was regarded as equivalent in effect to section of these nerves. These views have not received corroboration, and, as will be seen later, such manipulations as are necessary for the total removal of the canine gland, may be carried out with no effect whatsoever upon blood pressure or pulse rate, as shown by a kymographic tracing kept during the course of the surgical procedure. Cyon's operations were limited to rabbits and were not conducted with the view of obtaining recoveries.

In 1898 and later, elaborate studies were made by Arnold Caselli[11] with the primary object of determining the functional interrelation between the hypophysis, thyroid and parathyroids. He was led to believe in an antagonistic relation between these structures, for parathyroidectomized animals were thought not to show tetany if the hypophysis was removed at the same time, and further, that tetany due to loss of the parathyroids would be checked by a prompt hypophysectomy. In the course of his experiments he removed the hypophyses from a number of frogs by a pharyngeal route, without eliciting any particular subsequent disturbance, though in a few cases there occurred tetanic or epileptoid symptoms comparable to those which were found to follow intracranial operations of other kinds on these same animals. The author makes no mention of post-mortem examinations or microscopical studies.

He operated likewise upon a series of rabbits by the buccal route, without success, owing to inevitable meningitis; and almost equally unsatisfactory were his later operations on dogs and cats. By a most difficult and complicated spheno-palatine approach he operated on a series of 19 animals, almost all of which promptly succumbed to operative complications. In a second series of 36 canine operations he adopted the buccal approach of Vassale and Sacchi. Only 3 of the cases in which infection could be excluded were presumed, from naked-eye appearances, to be total removals, and the animals lived 16, 21 and 22 days, respectively, showing symptoms similar to those recorded by Vassale and Sacchi.

In the partial removals he observed transient phenomena of a similar nature with subsequent restoration to a subnormal state not incompatible with life. In 1 puppy there was an arrest of development, as shown by a comparison of weight with a control animal. Despite the uncertainty of his operative results, Caselli ventured to accept Vassali's opinion that the gland was of physiological importance, it being necessary for normal development and its total loss being followed by autotoxic disturbances leading to coma not unlike that which may occur in diabetes.

The results of experiments conducted on similar lines were published in 1900 by Friedmann and Maas.[12] On gross examination it was found that 13 of their 18 animals had presumably been subjected to a complete hypophysectomy (no microscopic control). Six of the animals succumbed to operative complications of infection and hæmorrhage. Five of the survivers died at periods of from 2 to 38 days after the operation, no cause for death being found, though infection was considered probable. One animal was sacrificed after $3\frac{1}{2}$ months and there was no macroscopic evidence of remaining glandular tissue. The authors concluded that the hypophysis is not essential to life, and in a later paper (1902) Friedmann[13] emphasizes this opinion and denies the retarding influence upon growth due to the loss of the gland which Caselli had described.

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[7] Gatta: Sulla distruzione della ghiandola pituitaria e tiroide. *Gazz. d. osp.* 1896, N. 146, 1537.

[8] Biedl. (Discussion) *Wien. klin. Wchnschr.*, 1897, X, 196.

[9] F. Pineles: Die Beziehungen der Acromegalie zum Myxödem, etc. *Samml. klin. Vortr.*, Leipz., 1899, N. F. 242, 1423.

[10] A. von Cyon: Beiträge zur Physiologie der Schilddrüse und des Herzens. *Pflüger's Arch. f. ges. Physiol.*, 1898, LXX, 127-521. Die Verrichtungen der Hypophyse. *Ibid.*, 1898, LXXI, 431; LXXII, 635; LXXIII, 483; LXXIV, 42, 97; 1899, LXXVII, 215; 1900, LXXXI, 267.

[11] Caselli: *Pflüger's Arch. f. ges. Physiol.*, 1898, LXXIII, 385.

Studi anat. e sperim. sulla fisiopatologia della ghiandola pituitaria. *Reggio nell' Emilia, Tipogr. Calderini*, 1900.

Influenza della funzioni dell' ipofisi sullo sviluppo dell' organismo: nota preventiva sulla fisiopatologia della ghiandola pituitaria. *Riv. sper. di Freniat., Reggio-Emilia*, 1900, XXVI, 176, *Ibid.*, 1900, XXVI, 486.

Étude anatomique et physiologique de la glande pituitaire. *Bull. Soc. de méd. de Gand.*, 1901, LXVIII, 311-313.

[12] Friedmann and Maas: Ueber Extirpation der Hypophysis Cerebri. *Berl. klin. Wchnschr.*, 1900, XXXVII, Nr. 52, 1213-1215.

[13] Friedmann: Noch einige Erfahrungen über Extirpation der Hypophysis Cerebri. *Berl. klin. Wchnschr.*, 1902, XXXIX, 436-438.

Lomonaco and Van Rynberk in 1901 [14] reported certain experiments performed on dogs and cats by an operation through the cranial vault similar to that employed by Gley, with an attempt to destroy the hypophysis by a needle introduced directly through the cerebrum. Though in only a small proportion of the cases was the gland apparently destroyed, the authors nevertheless concluded that it is not essential to life and that the unfavorable results of hypophyseal experiments were due to inevitable injury of important portions of the neighboring cerebrum.

Similar conclusions were reached by Gaglio in 1900 and 1902 [15] as a result of operations carried out upon frogs and toads by a buccal method. In the 2 frogs which survived from 1 to 3 months the removal of the gland appeared to be complete, but no microscopic examination was made. The main object of his research was to test the hypotheses of Cyon, with which he disagreed.

Pirrone in 1903 [16] reported his attempts to remove the canine gland by the spheno-palatine route which had been so unsuccessful in Caselli's hands. In view of the difficulties and uncertainties of this procedure he naturally attributed many of the post-operative phenomena to trauma rather than to loss of the gland, these phenomena consisting chiefly of variations in pulse, temperature and respiration. He nevertheless observed in 6 of his cases symptoms which we recognize to-day as manifestations of apituitarism—the characteristic depression, rigidity of the extremities with spastic gait, curvation of the spine and fibrillary twitchings, leading to cachexia and death. His conclusions were: (1) that all the phenomena consecutive upon hypophysectomy should not be attributed to disturbance of the function of the pituitary gland; (2) that absence of hypophyseal function accounts for the disturbance of motility, the psychic depression, the rapid emaciation, cachexia and death; (3) that the cardio-vascular, respiratory and thermic phenomena are the consequences of operative traumatism; (4) that removal of the hypophysis does not modify the composition of the urine; (5) that although the mechanism of hypophyseal function is not at all well understood one may say nevertheless that the gland is of vital importance; for, whereas a partial lesion of the organ may be compatible with life, its total removal leads to death.

Out of a series of 25 canine operations reported in 1903-1904,[17] Dalla Vedova, like most of his predecessors, lost a majority (21) of the animals from operative complications. Two of the survivers were sacrificed at a late period, and no macroscopic traces of the gland were present. Microscopic studies were not made as controls, an omission which the author himself notes; and in his second paper he calls attention to the fact that in the 2 survivors of his series originally reported as "totals" the microscope had revealed notable traces of remaining glandular tissue. His original conclusions, therefore, that animals might survive after a total hypophysectomy, were reversed in his second paper.

Brief mention was made in 1904 by Eiselsberg [18] of the fact that in an effort to reproduce acromegaly he had extirpated the hypophysis from a number of kittens by a buccal operation. One of the animals lived 10 days, but the others succumbed soon after the operation, supposedly from the immediate effects of the surgical procedure.

Fichera, in 1905,[19] reported the results of operations on 40 chickens, conducted by a retropharyngeal route through an incision in the hyoid region. The incision was made alongside of the pharynx without opening its cavity, thus lessening the danger of infection, and the attempt was made to destroy the gland with a cautery. In his 40 cases there were 29 recoveries, the greater number of which were sacrificed after some months. Four of these were regarded as microscopically complete removals. No constant or characteristic symptoms were noted and the author concluded that in chickens the hypophysis is not essential to life, though its complete removal may retard development.

By far the most important contribution to the subject was made in 1908 by Paulesco of Bucharest.[20] After some fruitless preliminary attempts 10 years previously to reach the dog's hypophysis by a buccal route, this physiologist, in collaboration with a surgeon (Balacesco), evolved an intracranial method of approaching the gland by the temporal route, applying what has of late years come to be a new principle for operations within the skull—namely, cerebral dislocation for the purpose of exposing parts otherwise inaccessible. In Paulesco's procedure both temporal muscles were detached from the skull and reflected downwards, permitting the establishment of a generous bilateral opening both in bone and dura. This made it possible to introduce an elevator under one temporal lobe, and to lift the brain sufficiently to expose the dangling pituitary body without cerebral injury or compression, owing to the accompanying dislocation and protrusion of the opposite hemisphere through its overlying bone defect. It can be readily understood that this operation, though complicated and delicate, represented a notable improvement over all the earlier ones, in view of the excellent exposure of the gland which it permitted and the lessening at the same time of the risks of infection which had been such a drawback to the buccal procedures.

In Paulesco's long series of hypophysectomies, 24 proved to

[14] D. Lomonaco and Van R. Rynberk: Richerche sulla funzione della ipofisi cerebrale. *Riv. mens. di neuropat. e psichiat.*, March and April, 1901, No. 9, p. 2.

[15] Gaglio: Recherches sur la function de l'hypophyse du cerveau chez les grenouilles. *Arch. ital. de biol.*, 1902, XXXVIII, 177-187.

[16] Pirrone: Contributo sperimentale allo studio della funzione dell' ipofisi. *Riforma med.*, 1903, XIX, No. 7 and 8, 169-175, 205-209.

[17] Dalla Vedova: Per la funzione dell ipofisi; nota preliminaria. *Boll. r. Accad. Med. di Roma*, 1903, XXIX, 150-160.

Per la funzione dell' ipofisi cerebrale; nota seconda. *Ibid.*, 1904, XXX, 137.

[18] v. Eiselsberg: (Discussion) *Verhandl. d. deutsch. Gesellsch. f. Chir.*, 1904, XXXIII (Kleinere Mittheil.), 111.

[19] G. Fichera: Sulla distruzione dell' ipofisi. *Sperimentale. Arch. di Biol. norm. e patol.*, 1905, LIX, 739-796.

[20] N. C. Paulesco: L'Hypophyse du Cerveau. Vigot Frères, Eds. Paris, 1908.

be *total,* the average duration of life of all cases being 24 hours. He made a second grouping of 7 *partial* hypophysectomies, comprising those cases which at operation were supposed to be total, but which the microscope subsequently showed to be incomplete. He formed the opinion that animals may live for a longer or shorter time according to the size and vitality of the remaining glandular fragment: two of the partially hypophysectomized animals survived for 5 months and a year respectively without exhibiting any observable deviation from the normal.

Removal of the *anterior lobe alone* (7 cases) he found to be equivalent to removal of the entire gland: loss of the *posterior lobe* (5 cases) led to no appreciable disturbance whatsoever: and separation of the *hypophyseal stalk* (6 cases) from the base of the brain amounted to a complete or to a nearly complete removal, as the case might be.

Paulesco's experiments were carefully controlled by performing the customary manipulations without the final step of removal of the gland, showing that the fatalities were not due to the opening of the third ventricle or to other cerebral lesions brought about by the surgical procedure. Careful post-mortem histologic studies of the base of the brain and contents of the sella turcica were made in all cases. In view of the importance of this contribution, his final conclusions may be given in his own words:

> L'hypophysectomie totale est suivie, à bref délai, de la mort de l'animal. La durée moyenne de la survie, chez le chien, est de 24 heures.
>
> Quand la survie est plus longue (elle peut même être indéfinie), c'est que des débris de la portion épithéliale de l'hypophyse (parfois minimes et même microscopiques) ont échappé à la destruction et sont demeurés vivaces,—ainsi qu'il arrive dane ce que nous avons appelé l'hypophysectomie presque totale.
>
> L'insuffisance du fonctionnement de l'hypophyse, à la suite de l'hypophysectomie totale ou presque totale, *ne se manifeste par aucun symptôme particulier et caractéristique.*[21]—et, dans les cas de survie prolongée, il ne se produit aucun trouble trophique appréciable au niveau des extrémités (muceau, membres). . . . .
>
> En résumé, l'hypophyse est un organe indispensable à la vie, son absence étant rapidement mortelle.
>
> Des diverses parties qui la constituent, la plus importante, au point de vue fonctionnel, est la couche corticale du lobe épithélial.

A few months after Paulesco's publication (1901) Gemelli[22] made record of a series of feline buccal operations by a method similar to the original procedure of Vassale and Sacchi. Eight of the animals survived and were sacrificed at periods varying from 6 months to a year. Of these, 7 were shown by most careful microscopic examination of the base of the brain and the sella turcica (decalcification) to have been subjected to a complete hypophysectomy. In one of the animals a certain amount of pars intermedia was found containing many small colloid vesicles. No especial symptoms were noted, with the exception of polyuria and polydipsia through the first few days and a subnormal temperature for the first 24 hours. Gemelli concludes therefore—Paulesco's observations to the contrary—that the gland is not essential to life, but that it possesses a certain compensatory function, the anterior lobe having some antitoxic properties and the posterior lobe some influence upon renal secretion. These studies of Gemelli's we have repeated, with results which will be given in a later paragraph.

Livon (1909)[23] performed a number of operations by the temporal route, making the serious surgical omission of not opening both sides of the skull. His primary object was to investigate the excitability of the hypophysis to various stimuli; but a few supposedly complete removals were saved for observation, the average duration of life in these animals being 36 hours. The author concludes that the hypophysis is a vital organ and that, contrary to Cyon's belief, it is not directly excitable and is not an autoregulator of the circulation through its sensibility to pressure.

In the same year (1909) from this laboratory, Reford and Cushing[24] reported a series of 20 operations also conducted on the lines similar to those laid down by Paulesco. The results of these observations were regarded as confirmatory of his main contention that total loss of the gland in the canine is incompatible with life. There were no microscopic controls.

III. Analysis of these Earlier Investigations.

For the convenience of reference, the methods employed in these several investigations, together with their results, have been gathered in tabular form. As can be seen, there has been an even division of opinion in regard to the gland's importance, and in view of the methods used in conducting the researches, it is perhaps remarkable that any of the observers, before Paulesco, came to the conclusion that the structure is actually essential to life. Table I shows at a glance how rarely have been observed the two most important elements for the success of these studies—(1) an operative method which assures, with reasonable certainty, totality of removal without complicating cerebral injury, hæmorrhage or infection, and (2) a subsequent microscopic corroboration of its accomplishment.

By the trans-cerebral operation attempted by Gley and Lomonaco an assured destruction of the gland is, of course, an impossibility, and the unavoidable damage to the nervous system by such a procedure would, in any event, have confused hypophyseal symptoms beyond recognition. In the difficult sphenopalatine procedure introduced by Caselli, infections were almost inevitable, and after 19 attempts Caselli himself abandoned the method in favor of the buccal route of Vassale, which he modified in some respects. Pirrone's results were possibly less unsatisfactory, but it is evident from his description that traumatism played a large part in them.

The buccal route, as can be seen, has been the favorite one,

[21] Italics, ours.

[22] Gemelli: Ulteriore contributo alla fisiologia dell' ipofisi. *Sonderabdruch aus Folia neurobiologica*, 1908, II, E. Hekma, Groningen. Also; Sur la fonction de l'hypophyse. *Arch. ital. de biol.*, 1908, L, 157-174.

[23] Ch. Livon: L'hypophyse est-elle un centre réflexe circulatoire? *Marseille méd.*, 1908, XLV, 745.

[24] Reford and Cushing: Is the pituitary gland essential to the maintenance of life? *Johns Hopkins Hosp. Bull.*, 1909, XX, 105.

TABLE I.—RESULTS OF PREVIOUS INVESTIGATIONS.

Author.	Route.	Subject.	Successful total removals.	Microscopic confirmation.	Importance to life and its duration after removal.	Symptoms in fatal cases due to apituitarism.	Symptoms of hypopituitarism in long survivals.	Operative complications.
1 Michel 1881	Frontal.	Dogs, cats, rabbits.	(?)	......	......	......	......	......
2 Horsley 1886	(?)	2 dogs.	2 (?)	Omitted.	Not essential; 5-6 months.	......	None observed.	......
3 Dastre 1889	Buccal.	......	......	......	......	......	......	No operative recoveries.
4 Marienesco 1892	Buccal.	8 cats.	(?)	Omitted.	Three survivals; for 4, 5, 18 days.	Possibly observed; cf. emaciation and lowered temperature.	......	......
5 Gley 1892	Cranial vault.	1 rabbit.	......	Partial destruction.	......	......	......	......
6 Vassale and Sacchi 1894	Buccal.	23 dogs, 17 cats.	15 (?)	In one case.	Important and essential to life; 37 days in one case.	Evidently observed; clearly described.	Evidences of insufficiency.	Many complications.
7 Gatta 1896	Buccal.	4 cats.	4 (?)	Omitted.	Essential.	Possibly observed.	......	......
8 Biedl 1897	Buccal.	Cats.	(?)	Omitted.	Not essential; survivals 8-18 days.	......	......	......
9 Caselli 1900	a. Buccal.	Rabbits.	......	......	......	......	......	Unsuccessful.
	b. Spheno-palatine.	19 dogs and cats.	......	......	......	......	......	Unsuccessful.
	c. Buccal.	28 dogs.	3 (?)	Occasionally made.	Essential; survivals 16, 21, 22 days.	Evidently observed but confused by complications.	Recovery after transient symptoms; arrest of development.	Many infections; meningitis.
10 Friedmann and Maas .. 1900	Buccal.	18 cats.	13 (?)	Omitted.	Not essential; 3½ months.	Denied; deaths attributed to infection.	Growth retardation denied.	Fatal complications frequent.
11 Lomonaco Rynberk 1901	Cranial vault.	49 dogs and cats.	4 (?)	Omitted.	Not essential; 20 days.	Denied; deaths attributed to cerebral injuries.	......	Cerebral injuries.
12 Gaglio 1902	Buccal.	Frogs, toads.	2 (?)	Omitted.	Not essential; 47 and 95 days.	......	......	Infections and paralyses.
13 Pirrone 1903	Spheno-palatine.	Dogs.	6 (?)	Omitted.	Essential; 7-15 days.	Probably observed but confused from complications.	Recovery after transient symptoms.	Cerebral injuries; inconclusive.
14 Dalla Vedova 1903	Buccal.	25 dogs.	4 (?)	Omitted.	Not essential.	......	......	Operative complications in 84 per cent; 4 hæmorrhages; 11 infections.
Dalla Vedova 1904	......	......	......	Based on two survivals of 1903 series.	Probably essential.	......	Gain in weight in one case; not commented on.	......
15 Fichera 1905	Lateral pharyngeal.	40 chickens.	11 (?)	Made in four cases but not described.	Not essential.	......	Retarded development. (?)	27 per cent operative deaths.
16 Paulesco 1908	Temporal fossa.	52 dogs and cats.	24	Made.	Essential; 2 days. Fragments of gland found in all longer survivals.	Fully observed and described.	Recovery after transient symptoms of cachexia hypophyseopriva; gain in weight (not commented on).	Occasional cerebral injury.
17 Gemelli ..... 1906 and 1908	Buccal.	Cats.	7	Made.	Not essential; 6-12 months.	......	Transient symptoms for few days.	Meningitis, frequent.
18 Livon 1909	Temporal fossa.	39 dogs.	Few.	Omitted. (?)	Essential; 36 hours.	Observed. (?)	......	......
19 Reford and Cushing ... 1909	Temporal fossa.	20 dogs.	15 (?)	Omitted.	Essential; 24-48 hours.	Observed and described.	Recovery after transient symptoms, with naked-eye fragments remaining.	Occasional hæmorrhage.

having been employed in 11 out of the 19 researches, and yet all the authors have acknowledged the frequency of complications from hæmorrhage and infection which attend the procedure, and in many of the earlier experiments, as those of Maricnesco and Vassale, the cautery was resorted to as the uncertain means of destroying the gland. The reports of this method which deserve chief mention, as they include the greater number of presumably successful experiments, are those of Vassale, Caselli, Dalla Vedova and Gemelli.

The two former evidently described symptoms of fatal cachexia hypophyseopriva due to loss of the gland, and though the evidence does not seem in all cases particularly conclusive, they regarded the structure as physiologically important and possibly essential to life. Survivals for as long periods as they observed them, in the light of our present knowledge make it seem probable, particularly in the absence of microscopic controls, that the extirpations were incomplete, unless possibly very young animals were used. For example, in the 28 dogs of Caselli's later series, 7 of the 14 regarded as total removals succumbed to meningitis, 2 to hæmorrhage, 1 to the anæsthetic, and 1 to enteritis, leaving only 3 in which operative complications could be excluded, and these 3 survived for the unusually long periods of 6, 21 and 22 days, respectively. Of his 6 supposedly total feline removals there were 5 deaths from meningitis. Although it is apparent that definite hypophyseal symptoms were observed by Caselli as well as by Vassale, the clinical picture was too greatly confused by the frequency of operative complications to make their deductions at all convincing.

The experience of Dalla Vedova is illuminating, inasmuch as he was led to reverse his earlier statement to the effect that the gland was not physiologically essential. This conclusion he had based on the 4 survivals in his series of presumably total removals, but subsequent careful histological studies demonstrated the presence of remaining anterior lobe fragments in each of these animals Gemelli alone of these 4 observers concluded, from his series of feline buccal operations, that the gland is not essential. To this we will refer later.

It can be seen that only 4 of Paulesco's 15 predecessors in this work regarded the gland as important or essential having observed symptoms which we now recognize as being definitely attributable to loss of the gland, rather than to the surgical manipulations at the base of the brain or to secondary operative complications. In only 3 of the investigations had there been an attempt made to control the result by microscopic studies, and of these 3, Fichera alone concluded that the gland was unimportant. His work was done on fowls by a difficult approach which necessitated destruction of the gland by a cautery. No detailed description evidencing the thoroughness of the histological studies is given, and as he observed retarded development, as we have in our animals after "nearly total" removal, the suspicion is aroused that fragments of the anterior lobe must have remained. However, we have had no experience with the avian hypophysis, and until his experiments are repeated Fichera's claims must stand uncriticized.

It will be noted that Paulesco is the only author who had a large number (24) of successful extirpations which were controlled by histological studies. Even with the operation which he introduced, allowing clear exposure of the gland and permitting accurate manipulations, his microscopic examinations showed that in all permanent recoveries fragments of the gland had been left, even when at operation the enucleation had been supposedly complete. Thus Dalla Vedova's earlier demonstration that even minute fragments of the gland might support life received further confirmation. Paulesco's argument is most convincing and his main contentions have already been in a measure confirmed by 2 subsequent (confessedly incomplete) reports—one by Livon and one from this laboratory by Reford and Cushing—in both of which his operative method was followed in the main.

As Gemelli's later paper was published with full knowledge of Paulesco's results, which they directly controvert, and as his buccal operations were well executed and microscopically controlled, his results deserve especial consideration, but we have been unable to confirm them, as will be seen.

Although our chief interest has come to be centered in the altered physical condition of the animals surviving for long periods after a purposeful partial hypophysectomy—an aspect of the subject heretofore neglected—it has seemed nevertheless of paramount importance to finally settle this debated question of essentiality of the gland, and hence the first part of our personal report, after a full description of the canine operation of Paulesco, will be devoted to this subject-matter.

IV. The Surgical Procedure.

1. *Paulesco's Temporal Route.*—Regarding this method as the most consistently successful of any heretofore employed and particularly suitable for an approach to the canine hypophysis, a procedure was evolved based on the principles introduced by Paulesco and meeting at the same time our personal requirements. This we have used without variation in our series of over 100 cases.

The canine hypophysis lies in a shallow sella turcica, less closely embraced by the local pocket of dura in which it rests than is the case with many other mammals. Hence with proper elevation of the temporal lobe the structure becomes accessible from its lateral aspect. This anatomical characteristic of the gland does not hold true for the cat or rabbit, for in both of these animals it occupies a deep meningeal pouch, the walls of which are channeled by sinuses, the chance injury to which would render further clean-cut manipulations impossible. Indeed, owing to a similar anatomical arrangement, the gland is far less accessible in old than in young dogs, and it was this fact which led us, in spite of their smaller size, to prefer young animals for purely surgical reasons—a matter which proved to be of importance, as we shall see.

The dog's skull possesses a broad temporal exposure which allows of fairly easy access to the inferior surface of the temporal lobe and hence to the sella turcica, but an attempt to elevate this lobe sufficiently to gain a clear view of the structure concerned leads inevitably to cortical injury, bleeding and operative confusion at the outset. In the presence of a large contralateral opening in bone and dura, however, the opposite

hemisphere will protrude sufficiently to allow the temporal lobe on the side of the approach to be lifted without risk of local cortical damage or of producing general cerebral compression. This is the principle of cerebral dislocation.

The age of the animal is of importance in other respects than mere enucleability of the hypophysis, for in young dogs all the steps of the operation are more easily performed. The temporal muscle is more readily separated from the bone, the cranial diploic sinuses are undeveloped so that in making the bone defects less blood is lost, and the dura is much less adherent and friable. For a long and delicate operation these things combine to permit a shorter and dryer operation with a better ultimate exposure of the gland. The difference in results of operations performed on old and young animals will be alluded to later.

In all of our canine operations we have followed a surgical technique, the exact counterpart of that which would be applied to intracranial operations on human beings. This implies skillful anæsthetization, a complete surgical equipment, proper sterilization of supplies and instruments, the wearing of gowns and gloves by the operator and assistants—indeed all that goes to make an operation safe and the possibility of infection remote (Fig. 1). Ample surgical experience, too, especially in so far as it relates to the tricks of controlling hæmorrhage and avoiding cerebral injury in intracranial work is desirable; for, owing to difficulties from the small canine field of operation, the surgical risks on this score are greater than would be the case with man.

In our earlier cases we had an occasional wound infection involving skin or muscle layers, but never a fatal meningitis. In the last 70 or 80 operations healing has taken place by primary union, and in the occasional early death of a totally hypophysectomized adult there were no evidences of infection. In our earlier experiences likewise, animals (not included in the series), particularly old adults, were not infrequently lost owing to uncontrolled hæmorrhage from vessels in the neighborhood of the hypophysis—meningeal, cavernous sinus or carotid. This accident, even in our later series, has occasionally led to the abandonment of the operation and the sacrifice of the animal under the anæsthetic, but complications from hæmorrhage have become of rare occurrence since we have become sufficiently familiar with the steps of the procedure.

From the beginning the greatest care has been exercised in the avoidance of any possible injury to the brain. This object has been attained, partly through the employment of the rounded spatula used for the temporal lobe elevation and partly owing to the contralateral cranial opening which permits of dislocation. Though Paulesco introduced the bilateral craniectomy for this purpose, he does not clearly state whether the dura is to be opened on both sides or only on the side of the approach. The efficiency of the dislocation is immensely increased by the doubly opened dura, and in fact there is no particular advantage in the additional cranial opening if the dura is left intact, as Paulesco must have learned. Livon, however, attempted his temporal operations with a unilateral opening.

Of the few special instruments which are useful (Fig. 2), a proper elevator is possibly the most essential. The form we have devised is about 1 cm. in width; it is slightly flexible so that it may be bent to fit beneath the temporal lobe, and the surface which is applied to the cortex is convex ("spoon-backed") from side to side, the edges and tip being rounded off. This rounding not only prevents the edges of the retractor from injuring pia-arachnoid and contusing the brain, in which case the soft cerebral substance, under pressure, extrudes about the instrument and obstructs the view, but also affords a channel of approach which is circular on cross section instead of semicircular and thus doubles the space for the operator's vision, necessarily restricted at best. A delicate hook-knife for the purpose of slitting the dura from within outward when making the incision deep in the temporal fossa, is useful and obviates the danger of cutting or injuring cortical vessels should the membrane be otherwise incised. The instruments used for the hypophyseal manipulations themselves are simply a pair of delicate strong forceps, bent in the middle so as to allow the operator to see along the blades, and a light spoon curette, which is useful when the posterior lobe alone is to be removed.

With the excellent view obtained by this operative method the gland, in the majority of cases, may be extirpated accurately and completely, or the delicate manipulations of partial removal may be performed with reasonable certainty. Whatever procedure may have been attempted, however, and presumably carried out, past experience has shown the necessity in all cases of a subsequent thorough post-mortem microscopic confirmation of its success. In the first report from this laboratory (Reford and Cushing) naked-eye appearances alone were relied upon. In the earlier cases of our present series, histological studies were made only when there was a reasonable doubt of totality, but we have come to regard it necessary to make serial sections in all cases.[25]

2. *The Operation.*—The animal should be weighed, its age estimated if not known, and preceding the operation it should be placed for a day or two in a metabolism cage so that the urinary output can be estimated and the standard amount of food and

[25] Great care must be taken at the autopsy to remove the brain without dislocating from the infundibular region any of the adherent blood-clot or possible fragment of gland which may have been overlooked at the operation. The routine performance has been conducted as follows: After reopening the incision and reflecting the temporal muscles the remainder of the calvarium is removed and the dura freely opened. The olfactory lobes are then scraped out of their pockets and the anterior portion of the brain lifted until the optic nerves come into view. They are divided as in the usual method of removing the brain of man. This brings into view the carotid arteries and hypophyseal region, and especial care must be exercised not to tear away the infundibular stalk from the tissue which may still occupy the sella turcica. All of this tissue is carefully freed from the bony floor, and still adherent to the base of the brain is removed intact with this entire structure. A block of tissue is then cut from the base of the brain including the optic chiasm and the entire infundibular region, and fixed in Zenker's or Bensley's fluid. The tissue is eventually embedded in paraffin and serial sections made and variously stained. The entire series of ductless glands, needless to say, is similarly removed and blocks preserved for histological study.

FIG. 1.—Showing general arrangement of field of operation. Operator wearing head-light.

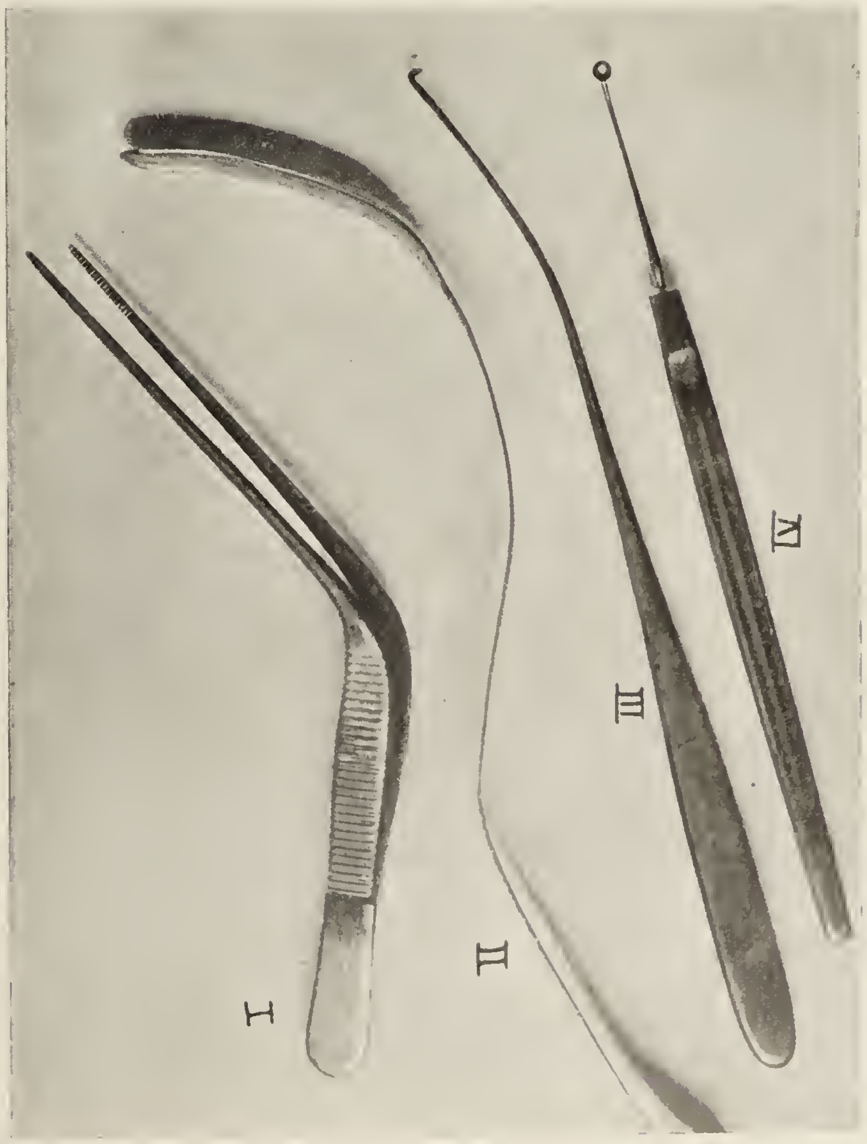

FIG. 2.—The few special instruments found useful (reduced one-third). I. Forceps for liberating gland from bed and picking it out by stalk. II. Spatula with spoon-shaped end for elevation of temporal lobe. III. Special cutting hook for deep incision in dura. IV. Spoon useful for removal of fragments or for dislocation of posterior lobe.

FIG. 4.—Drawing to show lateral defect, small dural incision and landmarks of gland in left lateral subtemporal approach. Tip of curved spatula enters between internal carotid and third nerve with gland in view.

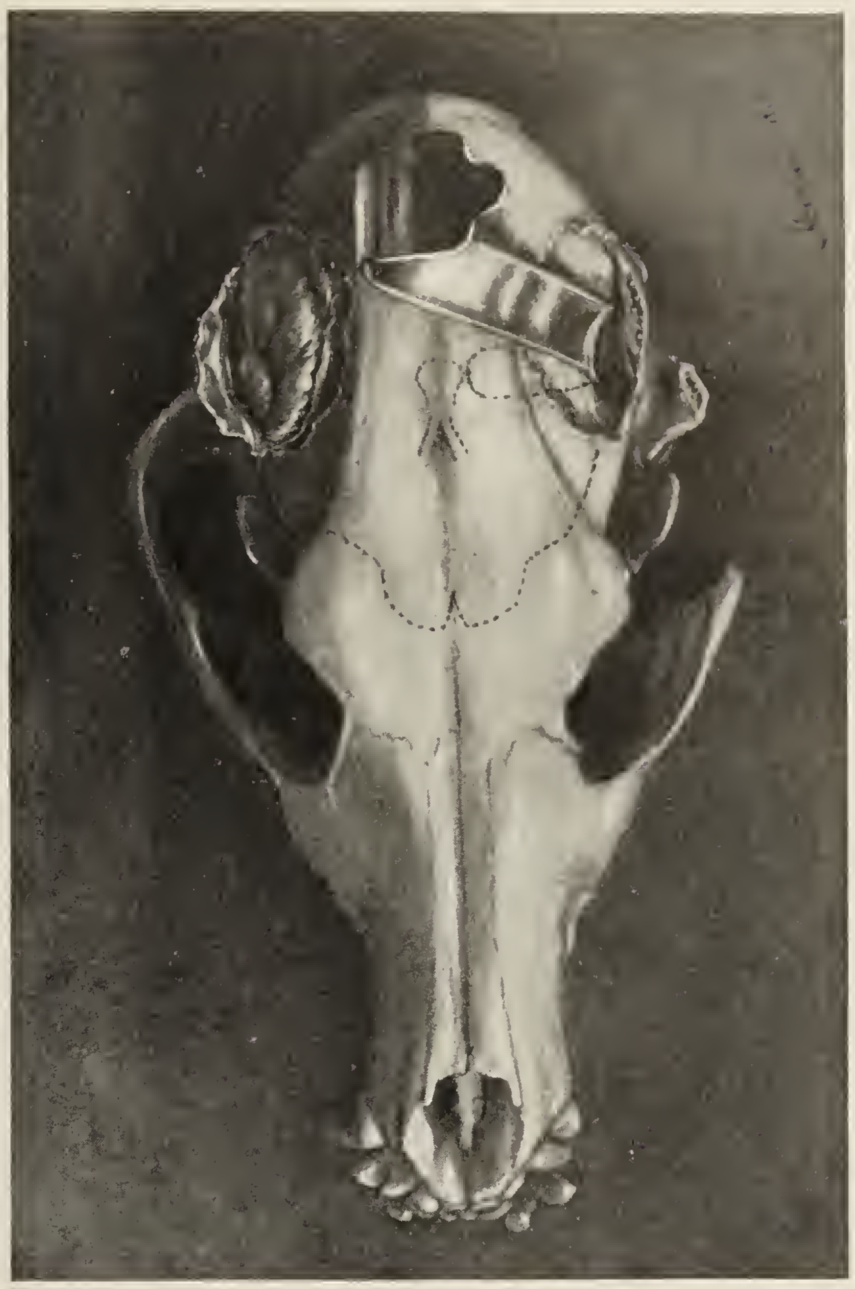

FIG. 5.—Contrast with Fig. 4. Upper view. Curved spatula in place, elevating temporal lobe. Note dislocation outward of right hemisphere through defect in bone and dura.

water regulated. After administering morphine from a quarter to half an hour before the operation, the drowsy animal is placed, belly down, on the operating table, with the head raised upon a wooden block hollowed out to fit the jaws. After securing the tips of the ears under the chin the scalp is carefully shaved from a point just behind the eyebrows well down upon the neck and out upon the ears on both sides (Fig. 3). Too energetic scrubbing is inadvisable: green soap, alcohol and bichloride solution suffice for the final preparation after anæsthesia (ether) has been administered. A piece of gauze wet in bichloride is then laid over the head. Dry sterile towels are spread over this and pinned to the skin in such a way as to leave only a narrow linear slit, through which gauze and skin are incised.

Fig. 3.—(Forty-eight hours after operation.) To show extent of shaved area and usual appearance of undressed wound before removal of sutures.

The layer of superficial muscles attached to the median cranial ridge are divided in the mid-line as far as the occipital crest, at which point the incision diverges in a Y as it passes down upon the neck. Concentric with, but about 5 mm. within, the upper line of insertion of the exposed temporal muscles (in order to leave sufficient margin for subsequent suture) an incision is made through the muscles, extending from a point near the orbit and ending at their posterior and inferior point of attachment, where a small artery is encountered. With a sharp elevator the temporal muscles and periosteum are then stripped downwards from their cranial attachments.

On the side chosen for the approach (we have invariably used the left: Figs. 4 and 5) it is necessary to strip the muscle far enough down to give access to the posterior zygomatic attachment. The zygomatic arch is then scraped in a forward direction until free from its muscular attachments, when it is divided with bone forceps, the arch broken as far forward as possible and the fragment dissected out of its bed. As is true of the Gasserian ganglion operation in man, this is an important step, for it permits of sufficient downward retraction of the thick muscle to assure a direct lateral approach with a minimum of temporal lobe elevation. Opening the animal's mouth will depress the coronoid process if this should interfere with the operator's view. On the right, the side of the counter-opening, there is no necessity for removal of the zygoma.

The denuded skull is trephined on both sides and the openings enlarged with rongeurs, wax being usually necessary to control diploic bleeding. The opening on the right becomes roughly oval in shape and averages about 3 by 3 cm. in a small dog—it can hardly be too large: on the left the bone is rongeured away, as far down as possible toward the cranial base so that the resultant opening has a more triangular form. The dura on the right is widely opened by an incision concentric with the bone defect: on the left, the side chosen for the approach, it should remain intact at this stage.

The special retractor is then introduced in the lower angle of the defect on the left, and as the dura is separated from the bone it is passed along the floor of the temporal fossa until the trigeminal line of dural attachment is encountered, where the membrane is strongly adherent. At this point the retractor is tilted and raised enough to stretch the dura, and with the hook-knife, which cuts from within outward an antero-posterior slit about $1\frac{1}{2}$ cm. long is made, allowing the retractor to be pushed in beneath the exposed temporal lobe (Fig. 6). No further opening of the dura is advisable on this side, for the relatively intact membrane serves as an excellent protection for the overlying temporal lobe during its subsequent elevation. At this stage there is always a more or less abundant escape of cerebrospinal fluid.

From this time on an electric head-light is essential, for the gland lies deep and monocular vision is all that can be brought into play. Introducing the retractor still farther beneath the temporal lobe, the unmistakable landmarks leading to the hypophysis are made out (Fig. 4). Running from behind forward and downward the glistening third nerve is easily identified, and in front, the internal carotid artery passing upward to the base of the brain. The tip of the spatula is directed between them and the hypophysis brought into view. The gland appears as an elongated, rounded body, pinkish-white in color, which seems to dangle from the infundibulum, suspended by its stalk and directed backward toward the sella turcica, to which it seems but slightly adherent.

If the hypophysis is to be completely removed the closed blades of the forceps are first passed behind and beneath it, freeing it from its posterior vascular attachments. The stalk is then grasped, care being taken not to include the internal carotid artery, and the gland is drawn out. It may often be obtained in one piece (Fig. 18), but if it tears and a portion is left lying in the sella turcica this fragment can easily be lifted out with the spoon curette. Occasionally the tip of the infundibulum comes away with the gland (Fig. 19), but if con-

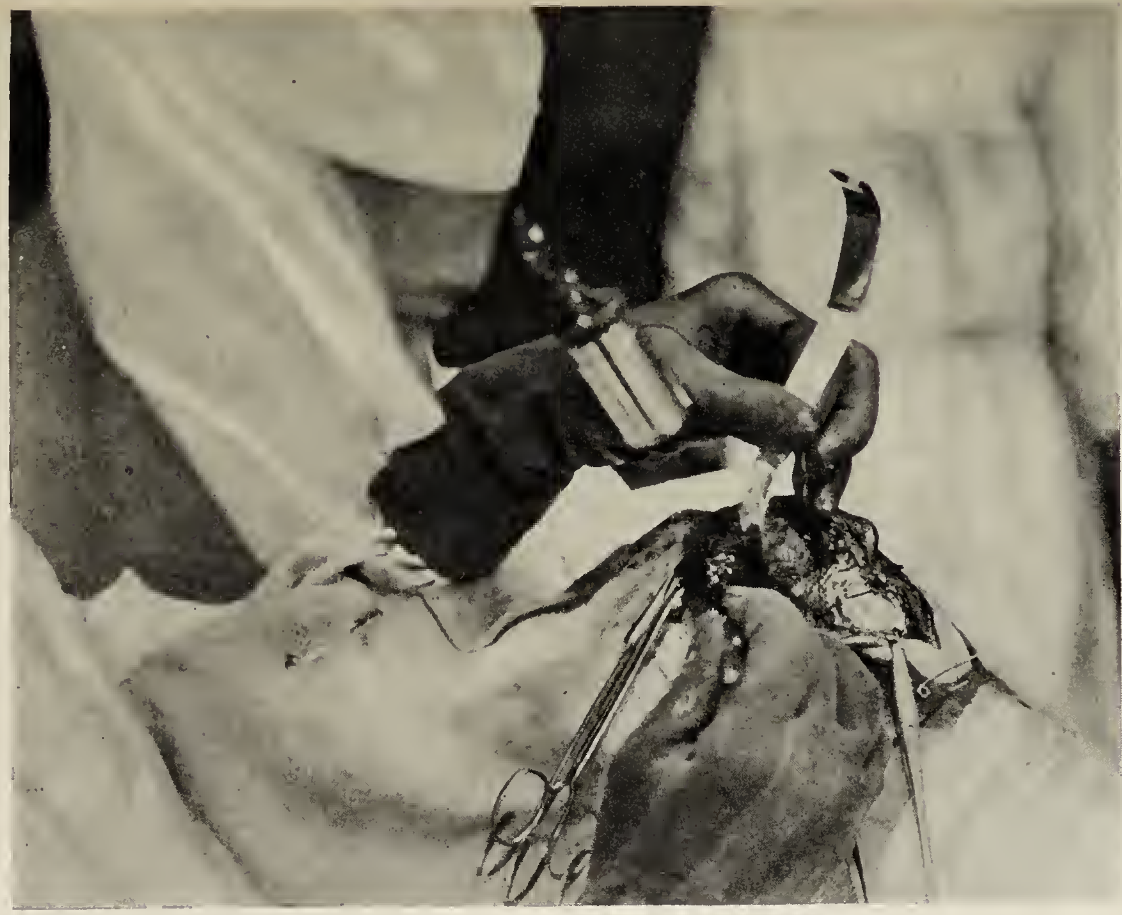

Fig. 6.—Near view of operative field, showing introduction of spatula with elevation of left hemisphere.

Fig. 8.—*Observation 80.* Mongrel puppy; 24 hours after partial anterior lobe removal.

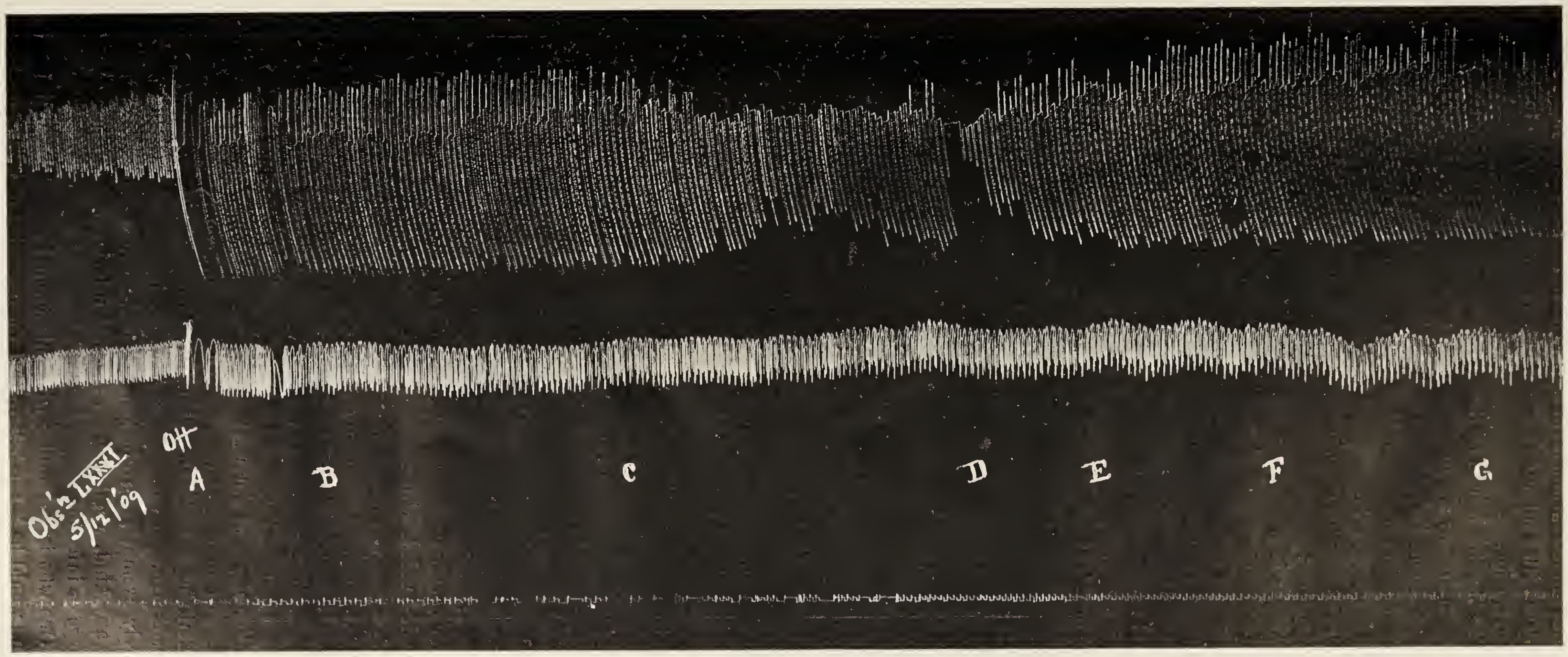

Fig. 7.—Record kept during course of partial hypophysectomy on *Observation 81* (cf. Fig. 38 and *Table VIII*), showing that the intracranial manipulation and removal of the gland produce no respiratory or vascular reactions. Following normal record, drum stopped at *A* during stages of operation preparatory to opening of dura. (*A-B*) introduction of elevator. (*B-C*) dura opened; escape of cerebro-spinal fluid; elevator introduced and temporal lobe elevated. (*C-D*) pars nervosa freed from posterior attachments and gland liberated. (*D-E*) stalk grasped and gland removed (presumably *in toto*); sponging. (*E-F*) third nerve intentionally manipulated and divided. (*F-G*) withdrawing from field; elevator removed, and brain released. (*G*) beginning closure.

ditions are less favorable the upper end of the stalk may remain in place with a minute fragment of pars anterior clinging to its anterior edge.

The bleeding caused by these procedures is moderate and can be controlled by the insertion of wisps of sterile cotton, which makes the best material for sponging. Needless to say, all manipulations must be made directly under the operator's eye: this is no place for a "blind" operation.

Of the possible complications, injury to the carotid is necessarily fatal; injury to a venous sinus, though controlled by packing, will prevent the satisfactory completion of the operation. Such accidents should be rare in experienced hands. In our earlier cases we occasionally so contused the third nerve as to cause permanent dilatation of the pupil, but of late this has rarely occurred. The same is true of injuries to the temporal lobe, which were occasioned in some of our early cases, leading to the peculiar rotary progression which characterizes a pyramidal tract lesion in the dog. The converging fibers of this tract lie very close to the surface of the temporal lobe at the most favorable point for elevation, and any cerebral laceration there is likely to produce motor symptoms, which might be easily misinterpreted.

When the field of operation appears dry after removal of the cotton packing the retractor is carefully withdrawn and the temporal lobe settles back in place, plastering the dura with its small incision against the skull. On the side of the counter-opening the dural flap is laid back but likewise need not be sutured. The divided muscles are reunited with fine silk sutures, care being taken to close all spaces where collections of blood might occur. The galea is brought together as a separate layer, and the skin closed with interrupted silk stitches. No drainage is used and the wound is left without a dressing, for bandages have been found to be unnecessary and they are annoying to the animal.

Since the operator should concentrate his attention steadily on the position of the retractor during the crucial part of the procedure, skilled assistants are, of course, a great advantage, and with their aid (Fig. 1) it is not unusual for the operation to be completed within an hour after the beginning of anæsthesia; nevertheless, with increased experience many of the later operations have been conducted (by Crowe or Goetsch) single-handed, with an anæsthetist.

3. *Effect of the Operation in Itself.*—In view of this extensive intracranial procedure, the question will naturally be raised: Are not the fatalities directly attributable to the operation itself rather than to the removal of the hypophysis? This was a personal criticism which carried much weight in the earlier stages of our work, when "neighborhood" injuries on the part of the nervous system were occasionally produced. Admitting it to be an elaborate, delicate and time-consuming performance, nevertheless our later series has been almost entirely exempt from operative or post-operative complications of any kind, whether from cerebral injuries or from hæmorrhage or infection.

One who is unfamiliar with intracranial procedures of this kind would be led to believe that the operation of itself would be tremendously disturbing in its effects. Many physiologists are under the impression that cerebral manipulations are invariably shock-producing affairs, and Cyon's description of the circulatory disturbances said to follow the mere mechanical stimulation of the pituitary body, which, therefore, was supposed to exercise some regulatory control over the cerebral blood supply, might make this result even more likely in the case of the operation under discussion. In all probability, were a bilateral opening not made, the necessary elevation of the temporal lobe would lead to a certain slowing of the pulse and rise in blood pressure—a physiological response on the part of the medulla due to compression alone. Such a response used to be observed during the act of exposing the Gasserian ganglion in man—a similarly conducted procedure, as has been pointed out, and one which necessitated temporal lobe elevation without the possibility of cerebral dislocation.

As an evidence, however, of the undisturbing nature of this hypophyseal operation and to show that no alterations in respiratory or vascular rhythm need occur during its progress, one of the hypophysectomies was conducted while a kymographic record was being taken (Fig. 7). Were further evidence needed that the operative manipulations of themselves cannot be responsible for the disturbances we are to describe, it should suffice to say (1) that they do not occur when the same manipulations are carried out and the gland crushed or fragmented but not removed—a performance which entails more loss of blood and more local trauma than a comparatively bloodless total extirpation; and (2) that 24 hours after all "partial" and most "totals" the majority of the animals are as lively and well as before (Figs. 8, 9, 10, 14, 15 and 23).

V. Personal Operative Experiences.

(a) total hypophysectomy.

Following the preliminary observations made in 1907 and 1908 by Reford and Cushing, we have made a more detailed study (1908-1909) of a much larger series of canine hypophysectomies conducted after the method described. Our primary object was not so much a further proof of the essentiality of the gland as it was (1) to attempt the tiding over of states of cachexia hypophyseopriva by feeding, injection or transplantation; (2) to observe the late consequences of partial removals, and (3) to study the effects upon the other ductless glands of hypophyseal lesions. However, in the course of these studies a certain number of total extirpations were made (21 in all) and as they were histologically proven to be total—a precaution neglected by Reford and Cushing—and as they bring out additional matters of interest, a tabulation of the cases may be given, to lead up to the more difficult and hitherto neglected study of the partially hypophysectomized animals suffering from grades of hypopituitarism. We have, furthermore, included in our series of 100 cases a number of the animals being studied at present (1909-1910) for other purposes by Dr. Emil Goetsch, making all told some 150 experiences, histologically corroborated, from which we may draw our conclusions.

As has already been stated, we soon learned that the opera-

tion was more difficult on old dogs—chosen at the outset owing to their larger cranium—and, unaware that age had any bearing on the final outcome, we began to select younger animals and finally puppies for the larger number of the operations. Some of the animals survived for so long a time before the onset of the expected symptoms of cachexia hypophyseopriva—some, indeed, supposedly (from an operative standpoint) subjected to a total removal failing to show any symptoms whatsoever—that for a time fresh doubts were aroused in our minds as to the actual essentiality of the gland.

As soon as we began to tabulate our results, however, on the basis of the microscopic studies, it was quickly appreciated that the cases fell into 2 groups, the life of the adults averaging 2 or 3 days, instead of 24 hours, as reported by Paulesco, whereas that of the puppies averaged 11 days, the longest duration after a confirmed total removal being 20 days. Viable anterior lobe fragments were found in every case of survival for a period of

FIG. 9.—*Observation 58;* mongrel puppy hound. Photograph taken the day after hypophysectomy. Note the animal licking his chops at sight of the proffered bone.

several weeks. It will be seen, however, that many of the animals, whose life depended on the retention of viable though minute fragments, possessed a greatly lowered resistance and often died from acute cachexia hypophyseopriva, even after long post-operative intervals, if called upon to withstand unusual conditions, such as infections or exposure or digestive disturbances.

The greater duration of life in the younger animals may possibly be due to their greater physiological elasticity, the other glands of internal secretion being able to assume, to a certain extent, the hypophyseal functions—a view receiving some support from the histological alterations observed in other organs, more particularly in the thyroid, and which we have interpreted as an hyperplasia. It is possible too that the pharyngeal "rest" of the gland which Haberfeld has described [26] as being fairly constant, may prove capable of a certain functional activity in young animals. But however we may attempt to explain the longer life of the hypophysectomized puppy, the clinical symptoms when they finally occur and the ultimate results of total removal of the gland in all of the 21 cases in our series and the 14 additional cases of Goetsch, have been the same, irrespective of age.

1. *Symptoms of Cachexia Hypophyseopriva (Apituitarism).*[27]

Though confused in many instances by complications attributable to surgical neighborhood injuries, certain of the manifestations of apituitarism nevertheless seem undoubtedly to have been observed during their experiments by Marienesco, Vassale, Biedl, Caselli, Pirrone, Paulesco, Livon, Reford and Cushing. After uncomplicated operations they are sufficiently characteristic, when once clearly recognized, to be thereafter unmistakable.

FIG. 10.—*Observation 94.* Mongrel collie, tugging at bone the day after a supposedly total hypophysectomy (subsequently proven partial) with cortical transplant.

As has been stated, the majority of the animals so promptly recover from the anæsthetic that they are soon on their feet and will lap water or milk in a short time: many of them, indeed,

[26] Haberfeld: Die Rachendachhypophyse, etc., *Beitr. z. path. Anat. u. z. allg. Path.*, 1910, XLVI, 133-232.

[27] In this section we are considering symptoms of so-called *cachexia hypophyseopriva* due to total loss of the gland leading to a state of anatomical *apituitarism*. We may, of course, meet with the same symptoms in suggestive and transient form, or even full-blown in case a persisting fragment of the gland has temporarily or permanently given out, producing transient or ultimate physiological apituitarism. Hence *apituitarism* and *hypopituitarism* overlap, but we have restricted the term *hypopituitarism* to the long-enduring states of glandular insufficiency not incompatible with the maintenance of life under favorable conditions. *Hyperpituitarism* is as yet a state which does not lend itself readily to

eagerly take solid food within 24 hours, in spite of the recent bilateral detachment of the more important masticatory muscles (Figs. 9, 10). Nevertheless, the adult animals, by the second or third day, though showing no change as yet in pulse, respiration or temperature, are, as a rule, noticeably less lively and responsive than those subjected merely to a partial removal. They are less interested in their surroundings, respond less readily to cajolery, are often irritable, and either return to their cages when given freedom or seek out and curl up in a quiet, warm corner. Certain changes in the urine, to be described, may be present.

A slight lowering of the body temperature is the usual inaugural symptom, but one of the first obvious signs is an unsteadiness of gait, with a certain stiffness of movement, particularly in the hind legs. This soon becomes exaggerated and the animal stands (Figs. 11, 12 and 26) or walks with a noticeable awkwardness, often showing a peculiar arching of

FIG. 11.—*Observation 36.* Adult fox terrier; a total removal 10 days after preceding heterogeneous transplant in bone marrow. Photograph taken 4 days after operation, showing typical attitude, with arching of back, etc., characteristic of onset of cachexia hypophyseopriva.

the back, suggesting at times, except for the incurved tail, the canine defæcation attitude. The body temperature continues to fall and before the end drops rapidly (6° to 8° C. in a few hours), until it may even approximate that of room temperature; particularly in the winter months the body may cool to an extraordinary degree—to 18° C. in one case, a loss of over

experimental study, but our results in this direction will be subsequently recorded.

These terms, representing states of *dyspituitarism*, as employed here have reference to the entire pituitary body, with full appreciation of the fact that the experimental states we are portraying are associated with disturbances of the pars anterior alone. When we possess a more complete knowledge of the gland and its various functions it will doubtless be necessary to construct a terminology which will indicate conditions of over or underactivity of each of the subdivisions of the gland.

20° C.—in spite of external coverings. The blood pressure falls and the pulse becomes feeble, irregular and unusually slow. Respiration, becoming largely diaphragmatic, slows uutil it may register only 3 or 4 to the minute (Fig. 13). Occasionally tremors are observed, but more characteristic are coarse rhythmic, spasmodic twitches of the body musculature. These are often inaugurated by an involuntary act, such as that of respiration, or may be elicited by the slightest external stimulus. Spasmodic opening of the jaws, with frothing, is frequently seen. The normal deep and superficial reflexes are retained to the end and often are exaggerated.

Lethargy becomes pronounced and the animal, difficult to arouse, becomes indifferent to the comforts of bedding or to the soiling from evacuation. Euthanasia seems complete, and though still conscious enough to respond with a movement of apparent recognition to the voice, there seems to be complete

FIG. 12.—*Observation 60.* Fox terrier puppy, 14 days after total removal (cf. Fig. 21). Symptoms of cachexia hypophyseopriva of 3 days' duration and more advanced than shown in Fig. 11. Photograph a few hours before death. Temperature 22° C. Respiration 6 to the minute (cf. Fig. 13).

anæsthesia to a painful stimulus, such as a pin-prick, or even to the taking of a direct blood pressure record from the femoral artery (Figs. 13 and 16). Finally a deep coma ensues and the transition from this state to death, occurring without a struggle, is so imperceptible that it is sometimes difficult to tell just when the end has come.

In commenting on certain resemblances between cold-blooded animals and the dogs in this state of subnormal temperature, Dr. Goetsch has called our attention to the fact that the heart, like the batrachian organ, will continue beating long after its removal from the body, and will contract on mechanical stimulus for an hour or more; also to the fact that the blood, after death, has an unusually bright red color, despite the unaerated condition one would expect in view of the marked slowing of respiration.

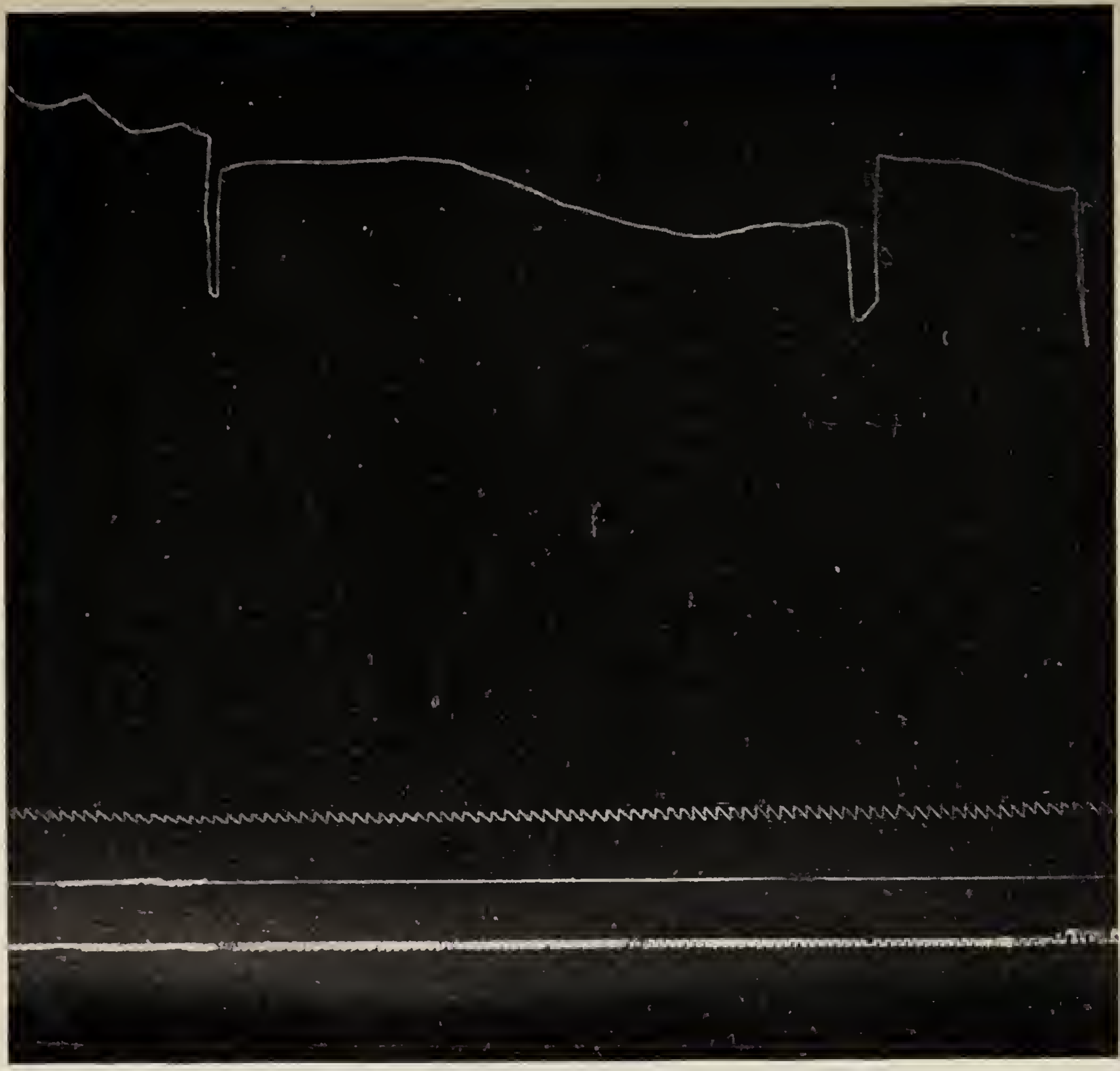

Fig. 13.—Fragment of record taken from femoral near terminal stage of coma in *Observation 60* (total hypophysectomy in a puppy); showing respiration 2-3 to the minute; pulse 40 and blood pressure 14 mm. Hg. Temperature at this time 22° C.

Fig. 14.—*Observation 64*. Puppy (4 months of age), playful and bright-eyed and apparently without symptoms 7 days after *total* hypophysectomy.

Fig. 15.—*Observation 89;* collie puppy. Photograph taken day after total removal, showing apparently normal animal eagerly dragging at a proffered bone.

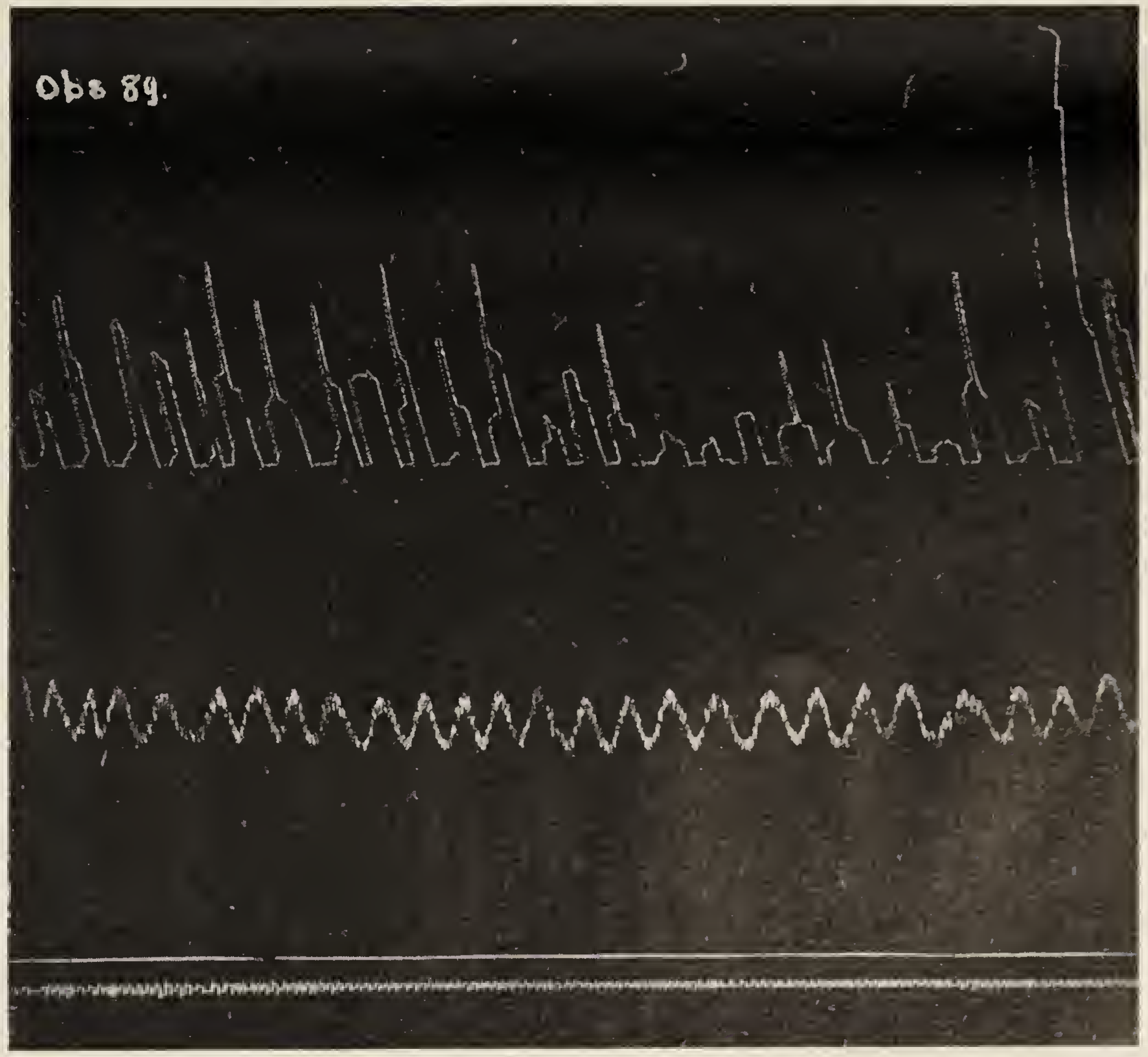

Fig. 16.—*Observation 89*. Record made just before death. Temperature 33.2° C.; respiration 10; blood pressure 23 mm. Hg., and pulse 150 (unusually rapid for this stage).

This entire transition from an apparent state of well-being may take place, particularly in adults, in the course of a few hours, though more often premonitory symptoms may set in a day or so before death. The more gradual onset is usual in the case of the younger animals, and, as will be shown later on, animals, after a nearly total removal, may show transitory symptoms which subside spontaneously or which may be interrupted by glandular transplantations or by injections of hypophyseal extract.

In order to emphasize the much longer duration of life in the young animals we have separated them from the adults in the tables to be given. This, however, remains practically the only distinguishing feature of the 2 groups (compare *Table II* and *Table III*).

2. *Results of Total Hypophysectomy in the Adult Canine* (*Table II*).—There prove to have been 13 cases; in all these the symptoms were allowed to run their course uninfluenced by transplants or glandular injections. As heretofore stated, the operation on old dogs, owing to the adherent and friable dura, is more difficult than on the young, and as most of them were performed early in our series, complications were more common. However, the results were controlled, as the case numbers indicate, by some additional observations on adults after we had become more expert.

In *Observations 6, 22, 44, 51* and *53* there were certain confusions from hæmorrhage, necessitating a piecemeal removal with an occasional temporal lobe and oculomotor injury: the remaining 9 operations were conducted without complication. Only 2 of the animals (*Observations 22* and *53*) succumbed in the first 24 hours, as did the majority (58 per cent) of Paulesco's 22 canine totals, which included young animals as well. On the other hand, only 2 of Paulesco's series lived over 36 hours, whereas all but 2 of ours survived this period, the longest duration being 5 days and the average nearly 60 hours.

The characteristic symptoms of apituitarism occurred in all cases. A marked diminution of the urinary output, even to anuria, was common, and a transient glycosuria was occasionally observed (*Observations 57* and *67*).[28] Thus in *Observation 57* the urine reduced Fehling's solution for 2 days after the operation, but failed to do so on the third day, and the urine in the bladder at autopsy 24 hours later had no reducing properties. In only 1 case (*Observation 44*) was there a wound infection, and this a superficial one.

Obvious histological alterations in the other ductless glands were first observed in the animals of this series, an enlargement with acute hyperplasia of the thyroid being the most noticeable change.

A typical protocol follows:

Observation 28 (*Table II*). An old, but apparently healthy male fox-terrier.

December 4, 1908 (2 p. m.). An uncomplicated operation by the usual method. Gland removed in one piece apparently intact. Prompt recovery from the anæsthetic.

December 5 (9 a. m.). Has entirely recovered from the effects of the operation. Has taken milk and water. Movements deliberate but otherwise normal. Left pupil dilated, showing operative contusion of third nerve, but no tendency to rotary progression due to temporal lobe and pyramidal tract injury: no arching of the back. Takes an interest in his surroundings and in other animals. Rectal temperature 38.7° C.; pulse 168; respiration 16.

(3 p. m.—24 hours after operation.) Much less active than in the morning. Lies curled up in a corner of the cage; is difficult to arouse. Will not stand or walk; tendency to arching of the back; refuses food and water. Rectal temperature 36° C.; pulse 160; urine for 24 hours 130 cc., no sugar.

(6 p. m.) Condition about the same as at last note. Rectal temperature has dropped to 35.2° C.; pulse 152.

December 6 (9 a. m.) Comatose; cannot be aroused. Reflexes present but sluggish. Body feels cold. Rectal temperature 26° C.; femoral pulse barely palpable—48 to minute, very irregular; respiration 10 to minute. No urine secreted for the past 24 hours; frequent watery movements of bowels and an increased flow of saliva.

During the morning the pulse gradually became weaker and more irregular; the respiration grew more infrequent and apparently ceased about 2 p. m.

Autopsy: Immediately after death. No hypophyseal tissue is evident on gross examination, and subsequent study of a series of microscopic sections through the base of the brain shows the removal of the pars anterior and pars nervosa to have been complete. The tip of the infundibulum is closed by a small organizing blood-clot, above which is a fragment of pars intermedia in a condition of evident hyperplasia.

The thoracic and abdominal organs are macroscopically normal. The same is true of the ductless glands. The thyroid alone was examined microscopically and appeared normal (at this time we were not making complete histologic studies of these structures).

3. *Results of Total Hypophysectomy in Puppies* (*Table III*).—In our personal (1908-1909) series no attempt was made to influence the course of the symptoms of glandular transplantation or injection in 8 of the 15 puppy extirpations histologically proven to be total. These 8 are grouped with 11 of the "proven" cases from the 1909-1910 series of Dr. Goetsch, which though hypophysectomized for other purposes are valuable in this connection also. Many of the animals were born and raised in the laboratory, so that their exact age was known, but they were all under a year, as indicated by the teeth.

As stated, the approach to the gland is easier in these younger animals, in spite of their relatively smaller size, but at the same time one is more likely to leave a small fragment of the upper edge of the anterior lobe than is the case with attempted totals in the adult. Hence, in view of their surprisingly long survival, it became necessary to serially scrutinize all sections from the infundibular block for the presence of even a minute viable fragment embedded in the strata of scar tissue. Not uncommonly such a fragment may be found (Figs. 36 and 42), although at operation the removal has seemed complete and although gross post mortem appearances also indicate totality of removal.

These anterior lobe fragments, which are unmistakable, owing to their cellular arrangement and the presence of acid-

[28] More careful attention has been given to the alteration in the urine in our 1909-1910 series, and Dr. Goetsch has found that a transient early glycosuria is nearly always demonstrable in all totals.

ophiles, adjoin the pars intermedia (Herring) cells which are necessarily left adherent to the infundibulum. The pars intermedia, however, seems to play no part in the question of duration of life, as will be seen when considering anterior lobe removals with preservation of the posterior lobe and investing pars intermedia.

The shortest duration of life occurred in *Observation 59,* a puppy 3 months of age, raised in the laboratory. The animal never entirely recovered from the effects of the operation, but remained inactive, and succumbed on the third day, with the usual symptoms—a slow, irregular pulse, low blood pressure, subnormal temperature (29° C.) and coma. In our series, the longest survival (*Observation 58*) was 20 days, and 2 puppies in the 1909-1910 series (Goetsch) lived 22 days. The average duration was something over 11 days.

The young animals recover promptly from the anæsthetic, and on the following day, as a rule, they are as lively and playful as before the operation. During the succeeding days many of the longer-lived animals show a noticeable gain in weight and seem normal in every way (Figs. 14 and 15) until the abrupt onset of symptoms of cachexia hypophyseopriva. This state is commonly inaugurated by a premonitory subnormal temperature, which may precede the other manifestations for a few days. Then follow inactivity and unsteadiness of gait, which usually foretell an exitus within 24 hours.

A typical protocol follows:

Observation 89. Collie puppy; age 6 months; weight 12 pounds.

May 28, 1909. Hypophysectomy without operative complications; apparently a total removal.

May 29. Bright and playful. Eats heartily (cf. Fig. 15). Temperature 38.6° C.; pulse 180; urine 500 cc., no sugar.

May 30. Apparently normal in every way. Temperature 38.6° C.; pulse 136; urine 280 cc.

May 31. Continues free from all post-operative disturbances. Temperature 38.6° C.; pulse 146; urine 280 cc.

June 1. Regularly empties his food pan, but nevertheless has lost one quarter of a pound in weight. Temperature 38.5° C.; pulse 100; urine 120 cc.

June 3. Continues to be lively and responsive. Temperature 38.3° C.; pulse 80, regular; urine 130 cc.

June 4 (8 a. m.). Sudden onset of symptoms of hypophyseopriva. Refuses food. Has lost all tendency to playfulness; lies sleeping in a corner of the cage; is difficult to arouse, but will walk slowly around the room when placed on the floor. Has marked arching of the back. Temperature 36° C.; pulse 92, barely palpable.

(2 p. m.) Perfectly comatose; lying at full length. Respiration slow and deep, largely diaphragmatic. 10 to minute. Temperature 33.2° C.; pulse 100, regular but difficult to palpate.

Without an anæsthetic being necessary a canula was placed in the right femoral artery and a record made of the blood pressure at 46 mm. Hg., with the pulse 150 (?) and respiration 10 (Fig. 16). Death occurred at 6 p. m. The animal's weight was 11½ pounds.

An immediate *autopsy:* No remains of the hypophysis were evident in gross and the serial sections failed to show any remaining anterior or posterior lobe tissue. A few pars intermedia cells undergoing hyperplasia remained attached to the infundibular stalk.

The abdominal and thoracic organs were normal, with the exception of what appeared to be an extreme fatty degeneration of the liver. The ductless glands showed: Thyroid, slight hyperplasia; adrenal, vacuolization of lower layer or zona reticularis clearly demarcating cortex from the medulla, which showed definite hyperplasia; thymus, though large, showed no recognizable change; pancreatic islets unusually large and distinct, with a peculiar arrangement of cells; ovaries, no recognizable change.

This protocol is that of one of the shorter-lived animals in this series, but the interval of well-being before the abrupt onset of the terminal symptoms is equally striking in the cases of those surviving for a period of 3 weeks.

A post-operative polyuria has been frequently observed in the puppies, contrasting with the opposite condition seen in the adults. Even in the 3-day case (*Observation 59*) 300 cc. was voided during the 24 hours after the operation, whereas 150 to 200 cc. is a fairly normal average. In each of the 7 remaining animals of the 1908-1909 series there was a polyuria varying from 500 to 1500 cc., which in some instances persisted for many days until the onset of the terminal symptoms, shown by a drop in body temperature, when the amount rapidly diminished, in some cases anuria preceding death. No reducing substance was observed in our cases, doubtless, in view of Dr. Goetsch's results in the 1909-1910 series, due to our failure to look for it during the first few hours after operation.

An indication of the reactionless healing is shown by the absence of post-operative pyrexia (cf. tables) in these animals: in only 1 instance (*Observation 65*) was there a day's febrile response of 1.4 degrees. The terminal drop in body temperature occurred in many cases during the last day of life, as in *Observations 58* and *70;* but this is not invariable as shown by *Observation 60,* in which the temperature reached its lowest registration at 22° C. after a gradual fall extending over ten days (Figs. 12 and 21). Efforts were naturally made in many cases to prevent this excessive lowering of body temperature, and though it could be raised many degrees—in some cases even to normal—by artificial measures, excessive panting would be brought on and the animals invariably seemed the worse for the attempt. It was observed, however, that the muscular tremors and spasmodic movements lessened with the rise in temperature.

4. *Hypophysectomy in the Cat by the Buccal Route.*—Although it is with the results of the canine operation that we are chiefly concerned, in view of Gemelli's contradictory experiences to which we have referred it may not be out of place to record certain observations made by one of us (Homans) in an effort to substantiate his findings. Owing to its wide and shallow mouth, the cat is the only available species in which even approximately accurate results may be expected by the buccal method of approach. A brief description of the feline operation follows:

Anæsthesia is administered with the patient on its back. A pad is placed under the neck so that the roof of the mouth slopes downward and forward: the jaws are held widely open and the tongue drawn out. The mouth is carefully cleansed with 50% alcohol. The soft palate is divided in the median line from the edge of the hard palate in front nearly to its posterior margin. A stitch is then taken on each side of this incision and the ends of the thread drawn out, holding the edges of the wound apart. Through this

opening the roof of the pharynx is exposed, cleansed and incised, the center of the 1½ cm. incision being at a point midway between the easily identified pterygoid processes. The edges of the incision are scraped back, exposing a median bony ridge, in which is a small opening for the passage of a blood vessel. The bone should be penetrated with a trephine, drill or guage, just posterior to this point, but the exact position of the primary opening is not of vital importance, since the hypophyseal pocket of dura is easily indentified and the opening can be enlarged backward or forward as needed. When finished (5 to 6 mm. in length by 4 or 5 in width) it should expose at least the anterior two-thirds of the gland and should extend for perhaps 2 mm. in front of it. The dural pocket is then incised and pushed to either side. A fine curette is passed into the back of the sella turcica, the posterior attachments of the gland divided, and the structure tipped forward as far as possible without rupture. Fine forceps are then passed in through the opening, one blade on either side of the stalk, and the gland drawn out. It rarely comes away intact, but the procedure causes so little bleeding that some at least of the remaining fragments can generally be picked out with the forceps or curette. The opening is then closed with bone-wax, the mucous membrane laid over it and the soft palate sutured.

Before the operation urotropin (gr. xxx) is given by a stomach-tube, and the comparative freedom from infection in our cases may be attributed in great measure to this precautionary measure.

Though eventual complete disintegration of the gland may generally be inferred when the infundibular opening in the floor of the third ventricle is seen with no hypophyseal tissue about it, there is always a possibility that fragments of anterior lobe may remain in the sella turcica detached from their normal position. Unless such a large opening is made as to greatly increase the danger of hæmorrhage or infection this possibility remains and constitutes the chief objection to the buccal operation.

In the 8 animals subjected to this operation the anterior lobe extirpation proved to have been total in only 2: the others on histologic examination showed remaining fragments of the gland, which in some cases were doubtless viable. All but 1 of the animals, nevertheless, succumbed in the course of a few days. In some of them the symptoms of cachexia hypophyseopriva were masked by those of infection, meningitis or hæmorrhage; but in the few cases free from surgical complications the symptoms were typical. Polyuria was constantly observed, glycosuria occasionally; and the low body temperature and motor disturbances preceding coma and death were in all respects identical with those of canine apituitarism.

A protocol follows:

Observation 84. Male kitten; weight 2 pounds.

May 19, 1909. Buccal operation without complication. Extirpation fragmented but apparently complete and showing infundibular opening. Urotropin by tube. Prompt recovery from ether.

May 20. Seems well and lively: takes nourishment.

May 21. Palate wound clean. Laps milk with urotropin. More quiet, but no meningeal symptoms. Temperature 38.4° C.

May 22. Onset of usual symptoms. Unsteadiness, muscular tremor, arched back, etc. Temperature 28.3° C.; deep, slow, diaphragmatic respiration. Constant urination, involuntary (?). With artificial heat temperature raised from 28° C. to 35.5° C. by noon, and to 37.7° C. by 5 p. m.

May 23. Condition about as yesterday, but very lethargic.

May 24. Died during night.

Autopsy: Wounds in palate and at base of skull clean. No meningitis or hæmorrhage. No gross evidence of retained hypophyseal fragments about infundibular stalk. Histological examination nevertheless shows a degenerated fragment of anterior lobe infiltrated with leucocytes and fibroblasts. Serial sections through entire infundibular region confirm total absence of viable anterior lobe cells. Many hyaline globules passing from remaining hyperplastic fragment of pars intermedia toward infundibular cavity.

Thoracic and abdominal organs macroscopically and microscopically normal. Ductless glands: no recognizable change; possible hyperplasia of adrenal medulla.

One animal which survived for a considerable time without showing symptoms, was sacrificed after 34 days, and, as anticipated, a fragment of anterior lobe of considerable size, which was viable, was found to have been overlooked at the operation.

Without going further into the details of these 8 cases, even this small experience with the buccal feline operation showed us (1) the frequency of complication (hæmorrhage and infection) by this method (3 cases); (2) the rarity with which at the operation totality of removal could be assured; (3) the fact that proven total removals in uncomplicated cases led to fatality in the expected interval with the usual symptoms of cachexia (2 cases), and (4) that survivals for a long period indicated incompleteness of removal.

5. *Criterion of "Total" Removal.*—To avoid any misunderstanding it seems advisable to indicate clearly just what we have meant to convey in the foregoing sections by "histologically proven total hypophysectomy." For control a median longitudinal section of the normal canine gland is shown in Fig. 17. Fig. 18 likewise shows a median section through the intact gland after extirpation in *Observation 63*, and Fig. 19 the base of the brain from the same animal as removed after death 4 days later. By no means does the gland always come away as intact as the one here shown, though probably this has been accomplished in 50 per cent of the observations planned to be total removals. The infundibulum, as can be seen, is open, and fragments of pars intermedia underlie the nervous tissue still constituting the floor of the third ventricle. It is obvious (Fig. 17) that in grasping the stalk even of the dangling gland [29] a fragment of anterior lobe could easily be crushed off and left in place (at the point B of Fig. 17) and Figs. 36 and 42 show how minute a fragment may serve the physiological needs. These anterior lobe fragments in the "partial removals" usually give evidence of hyperplasia (Fig. 36), and the same is true (Fig. 27) of the fragments of pars intermedia which inevitably remain even in the "total removals."

Whatever the function of the pars intermedia may be, it is of less vital moment to the individual than is the anterior lobe, as we shall see when considering the effects of partial removals. Further illustrations of the infundibular condition in other "totals" (*Observations 52* and *60*) are shown in Figs. 20 and 21, and a surgically supposed "total," which histologically was found incomplete, is given in Fig. 22.

The *conclusion* may be drawn from these experiences, in agreement with Paulesco, that the total removal of the hypophysis leads to a train of symptoms which characterizes no other known clinical condition and which, therefore, may safely

[29] The sections (Fig. 17) naturally show the gland in an abnormal position flattened against the base of the brain. The structure during life hangs away, a postural peculiarity which is accentuated by the surgical dislocation upwards of the cerebrum.

be ascribed to the loss of the gland, particularly in view of the fact that precisely the same operative manipulations which stop short of actual removal of the gland lead to none of these symptoms whatsoever.

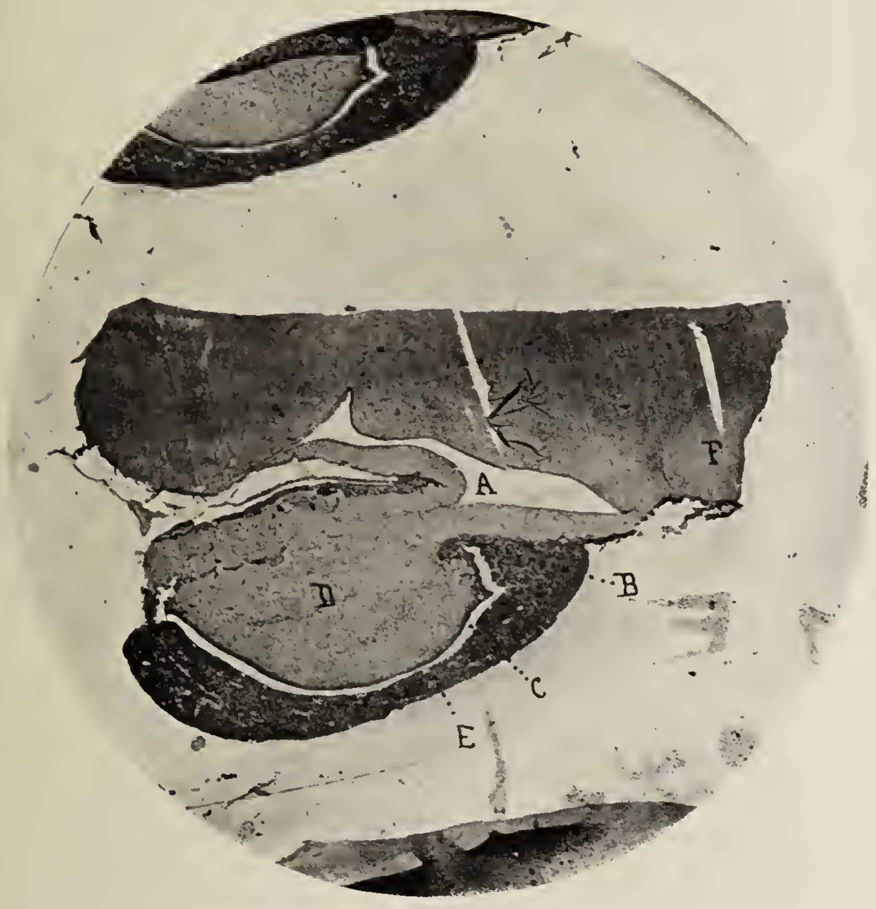

FIG. 17.—Normal control. Median section through base of brain and intact gland. For comparison with Figs. 18 and 19. *A*, third ventricle; *B*, junction of pars anterior and intermedia; *C*, cleft; *D*, pars nervosa; *E*, anterior lobe; *F*, optic chiasm.

FIG. 18.—Median section of the entire gland of *Observation 63* (*Table II*), as removed at operation (cf. Figs. 17 and 19).

This does not mean, of course, that animals with a retained fragment of anterior lobe will necessarily remain entirely free from all manifestation of hypophyseopriva symptoms, for although we have evidence that an exceedingly small fragment may, under favorable circumstances, support life, nevertheless animals with a "nearly total" removal may succumb as promptly as the totals, provided the removal is physiologically complete, the functional activity of the fragment being inter-

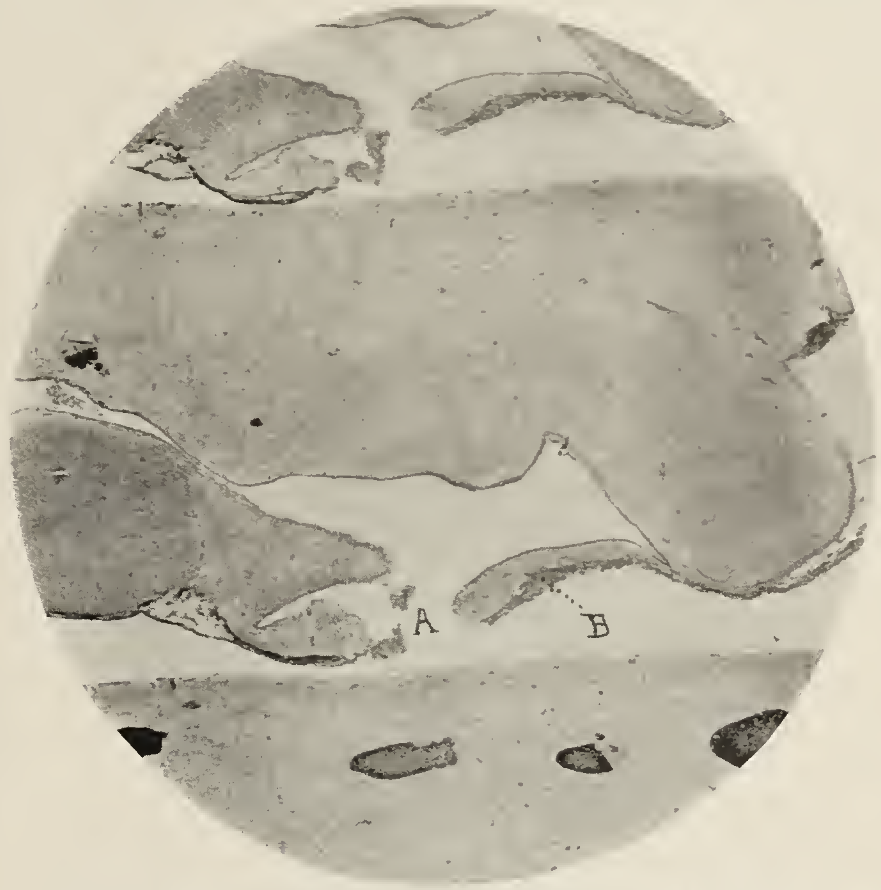

FIG. 19.—Median section through base of brain in *Observation 63* (*Table II*) 4 days after total hypophysectomy (cf. Figs. 17 and 18). *A*, open third ventricle; *B*, residual fragment of pars intermedia.

FIG. 20.—Median section of base of brain of *Observation 52* (*Table II*) 36 hours after adult hypophysectomy, showing slight extent of contusion.

fered with; and not infrequently, as we shall see, some of the nearly total removals show transient symptoms from which they may recover, which is never the case with anatomically total removals. We have found furthermore that the animals

with nearly total removals can be permanently tided over the period of threatened symptoms by glandular therapy, and it is possible that with improved methods of administration the same may be accomplished for the totals, but as yet, though we have been able to prolong life, we have not succeeded in the permanent saving of any of the "totals."

6. *Total Hypophysectomies Modified by Transplantations and Injections.*—It will have been noted that our experiences with something over 125 operations have given us comparatively few uncomplicated "totals," namely, the 15 questionable ones in the 1907-1908 series, the 21 adults and puppies of the 1908-1909 series (*Tables II* and *III*) and the 14 puppies of Dr. Goetsch's 1909-1910 series. This, however, does not include all of the "proven total" extirpations of our personal series, for the progress of the symptoms has been modified in a number of instances by transplantations or by injections in such a way as to make it inadvisable to include them in the

Fig. 21.—Median section 15 days after total hypophysectomy in *Observation 60* (*Table III*). Showing average amount of remaining pars intermedia, open ventricle and absence of contusion.

foregoing table, the primary object of which is to accentuate the duration of life in states of *unmodified* post-operative apituitarism.

The results of our 23 *transplantation experiments* have already been published.[30] The grafts were placed either under the rectus muscle, in the bone-marrow, according to the method of Kocher, or in the right cerebral subcortex exposed during the operation. We were much more favorably impressed by the latter method as being especially convenient for immediate isotransplantation of the removed gland. In 3 of these cases (*Observations 4, 13* and *99*) the hypophysectomy was subsequently proven to be total. In *Observation 13* the animal died in 48 hours after the usual symptoms, and the engrafted tissue was found completely necrotic. In *Observation 99* (protocol given, *loc. cit.*) an adult animal surviving the usual fatal period was sacrificed at the end of 18 days, no symptoms whatsoever, beyond a transient glycosuria, having been observed; a peripheral zone of normally staining, viable anterior lobe cells surrounded the necrotic center of the graft, and colloid bodies were abundant in the adjoining cerebral tissue. In *Observation 4,* on the other hand, transient symptoms of cachexia hypophyseopriva appeared on the second day, but subsided, and the animal was sacrificed on the 15th day, at which time the graft showed a peripheral zone of normal appearing anterior lobe cells with hyaline bodies, presumably from the pars intermedia, in the surrounding brain.

At the time of these experiments we were greatly surprised to find so narrow a peripheral zone of still viable cells, for we did not then realize how minute a fragment of anterior lobe suffices to maintain life under favorable circumstances. Had

Fig. 22.—Supposed total hypophysectomy after 48 hours. Showing adherent blood-clot in which remains a tag of pars anterior.

this been appreciated we might have looked more favorably on the condition of the bone-marrow heterotransplants engrafted before the hypophysectomy, for we regarded them at the time as so far degenerated as probably to be functionless. The condition of the immediate autotransplants of the surgically extirpated glands was better, due doubtless to the principle emphasized by W. S. Halsted as the result of his parathyroid experiences, namely, that an existing physiological deficit is an essential factor to a successful "take." In the few cases in which the homogeneous gland was implanted a day or two after the hypophysectomy its beneficial effects in tiding over symptoms of cachexia and thus prolonging life was more apparent than when it had been implanted a few days before the operation.

The crucial test of removing the graft itself from one of the

[30] Effects of hypophyseal transplantation following total hypophysectomy in the canine. *Quart. J. Exp. Physiol.*, 1909, II, No. 4, 389.

animals with a primary total removal, or of completing a partial hypophysectomy by a second operation was attempted several times. We were frustrated in both of these tests, on the one hand because in several of the animals from which the graft had been removed no symptoms occurred and we subsequently found a minute anterior lobe fragment at the base, and on the other hand because in a second-stage approach to the sella turcica it is almost impossible to secure a clear and bloodless view.

This portion of the work needs careful repetition and amplification, but from the 7 observations with grafts in cases of proven total removal we feel justified in the conclusion that there was a distinct prolongation of life through these means. We shall see later on that implantation of homogeneous grafts, when symptoms of cachexia hypophyseopriva arise after almost total removals, will often serve to tide the animals over this critical period.

Fig. 23.—*Observation 85.* Mongrel puppy 24 hours after posterior lobe removal. No symptoms. Eagerly expecting proffered bone.

Our *injection experiments* likewise were made upon a number of proven totals with results which we withhold for later comment.

(b) Partial Hypophysectomy.

1. *Effects of Posterior Lobe Removal.*—In view of the fatal consequences of removing the entire gland, the next step naturally was to determine which of the 2 surgically divisible lobes is the more essential to the maintenance of physiological equilibrium, so strikingly upset by the loss of the structure as a whole. In consequence of its well recognized physiological properties, akin in many respects to those possessed by the adrenal medulla, it would have been a natural supposition that the posterior lobe, with its epithelial investment (*pars intermedia*—Herring) would prove to be the essential fragment.

In the dog the spherical posterior lobe, owing to the well preserved cleft may be easily dislodged from its position in the cup-shaped pars anterior with little or no disturbance of this anterior portion of the gland, the only attachment of any importance being the few columns of anterior lobe cells which mark the transition between pars anterior and pars intermedia (Fig. 17).

Paulesco made 5 experiments of this nature and concluded that this portion of the gland is not essential to life. One of his animals died with convulsions 2 years after the operation; the other 4 lived from 13 days to 8 months, succumbing to an epidemic of broncho-pneumonia in his kennels. No symptoms were observed, with the exception of terminal convulsions in the one animal.

As will be seen by the accompanying table (*Table IV*) we have had in our 1908-1909 series 3 uncomplicated observations of this character, and these have been supplemented by several others in the 1909-1910 series.

In our series there were also many other cases in which, purposefully or accidentally, not only the posterior lobe, but some of the pars anterior was removed as well: these will be considered under a separate grouping (*Table VIII*).

Of our 3 unmodified (by transplantation) and uncompli-

Fig. 24.—*Observation 86.* Posterior lobe removal; normal condition 24 hours after operation.

cated cases, one (*Observation 25*) was sacrificed after 6 months. The animal during this period had a number of peculiar convulsive attacks with maniacal excitement. A more or less persistent erotomania also characterized the post-operative history; and the same has been true of one of the animals in Dr. Goetsch's 1909-1910 series—a condition of sexual activity, the reverse of that seen after loss or diminution of anterior lobe function.

Of the other 2 posterior lobe removals, *Observation 86* (Fig. 24), a puppy, seemed in normal condition when sacrificed on the 50th day. The blood supply of the anterior lobe must have been affected, as in the stalk separations (*Table VI*), for this part of the gland was almost completely degenerated, there being only one small focus of normal appearing cells. The animal had become fat, showing a gain of 3 pounds in weight. *Observation 85* (Fig. 23) died on the 23d day without any

of the symptoms of cachexia hypophyseopriva. The anterior lobe was in very good condition and all other organs were normal, except the liver, which was extensively degenerated and showed only scattered areas with fairly normal cells.

An illustrative protocol follows:

Observation 25 (*Table IV*). *Extirpation of posterior lobe; convulsions; erotomania; sacrificed after 6 months.*

December 4, 1908. Adult male bull terrier; weight 18¾ pounds. *Operation:* Total uncomplicated posterior lobe removal; no operative complications.

December 5. Bright and playful; eats heartily. Temperature 38° C.; pulse 160; urine 200 cc., no sugar; weight 18½ pounds.

December 6. Animal lively; appetite good. Temperature 38.6° C.; pulse 140; urine 300 cc., no sugar.

December 19. Wound has healed *per primam.* Seems normal in every way. Temperature 38.8° C.; pulse 140; urine 400 cc., no sugar.

January 17. Weight 20 pounds; temperature 38.6° C.; pulse 120; urine 320 cc., no sugar.

February 8. Continues apparently normal in all respects; allowed to run in paddock. Temperature 38.2° C.; pulse 90; urine 250 cc., no sugar; weight 20 pounds.

March 22. Since previous note animal has been in paddock, apparently in perfect health, though noticeably erotic. To-day he suddenly became very much excited; blindly running into the walls. Repeated severe convulsive seizures followed, with marked salivation. Was placed in a warm room and given ⅛ gr. of morphia.

March 23. Has entirely recovered. Three days later (March 26) again turned in the yard, though a nuisance owing to erotic tendencies.

March 29. Temperature 38.2° C.; pulse 96, irregular; urine 420 cc.; weight 18¾ pounds.

April 14. Appetite good. Temperature 38.6° C.; pulse 60, very irregular; urine 360 cc., no sugar. Erotomania persists.

May 10. Second series of convulsions similar to those of March 22; recovery within a few days. Temperature 37° C.; pulse 69, very irregular; no sugar in urine.

May 30. Temperature 38.4° C.; pulse 72; urine 280 cc.; weight 19½ pounds. Sacrificed under anæsthesia.

Autopsy: Body well-nourished; panniculus abundant. Brain and meninges appear normal on gross examination. Pars anterior intact, and though flattened is normal in appearance. Thyroids are slightly larger than normal and quite firm. Abdominal and thoracic organs appear normal.

Microscopical Examination: The portion removed at operation consists of the pars nervosa with its epithelial investment. The remaining anterior lobe is normal in appearance. There is a compensatory (?) hyperplasia of the remaining fragment of the pars intermedia and an unusually large number of colloid bodies are present in the brain tissue adjacent to the ventricle. Liver shows evidences of fatty degeneration (?). *Ductless Glands:* Adrenal, normal. Pancreatic islets, normal, though cells are possibly somewhat enlarged. Testis, tubules normal with active spermatogenesis; no change observable in interstitial cells.

In reviewing these few cases it is apparent that subnormal temperatures and other manifestations of cachexia hypophyseopriva have not been observed, and whether the maniacal and convulsive attacks and the erotomania can be safely looked upon as characteristic of posterior lobe removal will need further investigation. Certainly no symptoms of this kind have occurred among the large number of cases of posterior, combined with partial anterior lobe removal.

We have not observed any lowering of blood pressure or diminution in the urinary output—symptoms which might be expected in view of the known action of extracts of this part of the gland. One must bear in mind that fragments of pars intermedia which evidently undergo hyperplasia (cf. Fig. 27) are necessarily left behind no matter how clean-cut the operation may be, and an abundance of hyaline is to be found in the channeled spaces leading from these fragments to the infundibular cavity. In this respect the posterior lobe removals are necessarily less conclusive than those of the anterior lobe, but the following will show that the posterior lobe, even in its entirety, will not suffice to maintain life.

2. *Effects of Removal of the Anterior Lobe Alone.*—Dislocation and removal of the posterior lobe without accompanying damage to the pars anterior, though less easily accomplished than removal of the entire gland, nevertheless is a comparatively simple operation. Much more delicate and difficult, however, is the reverse procedure, namely, total removal of the pars anterior, leaving the posterior lobe in place, still attached to the infundibulum and with its circulation intact.

In 6 of our 9 attempts we failed in our object, as shown by subsequent histological studies. These animals all survived for periods of a number of days to 6 months, and histological studies showed viable microscopic anterior lobe fragments in each instance. They consequently have been transferred from this group to *Table VIII.*

In 3 instances (*Table V*) the extirpation was proven total, with a clinical picture identical with that following a total hypophysectomy.

A typical protocol follows:

Observation 7. *Microscopically proven total removal of anterior lobe with intact posterior lobe in place. Death in 68 hours from cachexia hypophyseopriva.*

Adult fox-terrier.

October 8, 1908. Operation: No complications aside from the usual bleeding of an adult craniotomy. Excellent view of gland, which was carefully manipulated until the two lobes were dangling separately. Cup-shaped anterior fragment removed apparently intact, leaving posterior lobe in place. Prompt recovery from anæsthetic. Animal walked downstairs to kennel 2 hours later.

October 9. No symptoms other than slight dilatation of left pupil. Takes water and milk eagerly. Active and shows no disturbance of gait. Temperature 39.2° C.; pulse 140; urine 420 cc., no sugar.

October 10. Wound in perfect condition. Animal inactive, dull and unreponsive. Refuses solid food. Polyuria (amount not measured; no sugar) and polydipsia. Temperature 37.2° C.; pulse 116.

October 11. Lethargic in early morning and refuses food but drinks freely. Subnormal temperature (32° C.); pulse feeble and irregular (60); respiration slow and deep, each inspiration accompanied by a spasmodic contraction of the diaphragm and abdominal muscles. Animal in deep coma by noon and death occurred suddenly at 2 p. m., with copious watery evacuation of the bowels; no convulsive seizures.

Autopsy: The posterior lobe was found in place; blood supply and stalk intact. No naked-eye evidence of pars anterior. Thyroid not examined; other organs appear normal.

Microscopic examination of the base of the brain shows complete removal of the anterior lobe. Pars intermedia cells appear active,

invading the pars nervosa in many places; acini contain an abundance of colloid, and hyaline bodies in unusual number fill the tissue channels of the pars nervosa and extend to the ventricular floor (Fig. 30).

These cases furnish additional evidence that the anterior lobe, from the standpoint of physiological equilibrium, is the most essential part of the gland, for after its removal the post-operative symptoms and average duration of life are the same as those following a total hypophysectomy.

3. *Consequences of Stalk Separation.*—The surgical division of the hypophyseal stalk, completely separating the gland from its infundibular attachment, is regarded by Paulesco as equivalent to a total or nearly total hypophysectomy. His contention is based on the results of 6 observations in which the stalk was divided and the gland left in the sella turcica. Three of these animals succumbed within 20 hours following the opera-

FIG. 25.—*Observation 25.* Photograph of animal 5 months after removal of posterior lobe. Animal very lively and playful (difficult to photograph). No appreciable symptoms consequent upon operation, with possible exception of erotomania.

tion; the remaining 3 lived 6, 18 and 24 days, respectively. No mention is made, however, of the ultimate cause of death nor of the post mortem findings in any of these longer-lived animals of the series. The only protocol in full is that of an animal which succumbed in 20 hours, the hypophysis being found turgid, hæmorrhagic, and the cells in process of degeneration.

We have made 5 observations of this type (*Table VI*). Two of the animals (*Observations 20* and *35*) succumbed with all the symptoms of cachexia hypophyseopriva, 1 on the tenth day and the other on the 24th day after operation. In *Observation 20*, a puppy, the gland was completely degenerated, making the procedure equivalent to a total removal; and in *Observation 35*, an adult male, the anterior lobe showed but few cells which retained normal staining reactions. *Observation 83* (Fig. 26), also an adult, was sacrificed on the 28th day, owing to symptoms of distemper, and at autopsy a large part of the anterior lobe was found still viable. *Observation 90*, a puppy, was sacrificed on the 12th day, while in a normal condition for the purpose of studying the tissues, and *Observation 33* was successfully tided over a period of threatened cachexia hypophyseopriva by glandular injections. The protocol of this case follows:

OBSERVATION 33. *Separation of hypophyseal stalk. Symptoms of cachexia. Recovery after injections. Sacrificed after 5 months.*

December 18, 1908. Adult male fox-terrier. *Operation:* Usual procedure except that the infundibular attachment was merely divided, leaving the gland lying detached in the sella turcica. No operative complications; good recovery from ether.

December 19. Lively and in good condition but very vicious. Temperature 37.2° C.; respiration 14. Urine 880 cc.

December 20. Taking solid food. Pulse 120; respiration 12; urine 935 cc.

December 21. Temperature 38.1° C.; pulse 132; respiration 18, urine 950 cc., no sugar.

December 26. Takes nourishment well but is losing weight. Urine 730 cc.

December 29. Rapidly losing weight. Temperature 38.8° C.; pulse 144; respiration 10.

FIG. 26.—*Observation 83.* One month after stalk separation. Characteristic attitude (incurvation of tail and humping of back) with onset of cachexia hypophyseopriva, precipitated by attack of distemper.

December 30. Onset of definite symptoms of cachexia hypophyseopriva. Given subcutaneous injection of 10 cc. of a prepared 1 per cent solution of anterior lobe of the pig.

December 31. Injection repeated. Temperature 39.2° C.; pulse 128. Animal much brighter; restless.

January 1 to February 4, 1909. During this period *injections* of anterior lobe extract (pig or ox) were given almost daily, 20 in all. Improvement was slow but definite, despite an attack of distemper(?) lasting for about 10 days, after January 4. During the injections there was a more or less constant pyrexia of a degree or so; they were all well tolerated and produced no abscesses.

Marked improvement set in toward the end of January and the injections were discontinued February 4.

February 4 to March 1. A continued gain in weight during this period. Condition excellent, though an occasional slightly subnormal temperature.

March and April. Has been in paddock with other animals.

Apparently normal in all respects, though growing fat. There was a gain of 4 pounds in weight in the last month.

May 15. Has shown no further symptoms. Remains well and fat. Temperature 38.5° C.; pulse 100; weight 18 pounds. Sacrificed on this date.

Autopsy: The hypophysis is represented by a fibrous tag adherent to the infundibulum. Naked-eye appearances of all organs normal, except the thyroid glands, which seem hyperplastic. *Microscopic:* The hypophysis is more or less embedded in scar-tissue which adheres to the floor of the third ventricle. Such of the glandular tissue as remains is relatively small in amount, but there are areas of normal appearing anterior lobe cells, a few of the acini containing colloid, there being one large colloid cyst. The sinusoidal vessels are much dilated.

The posterior lobe is more normal in size, but the pars nervosa is invaded by pars intermedia cells, which are large and seem hyperplastic (Fig. 27). There is an over-abundance of hyaline throughout the pars nervosa and many colloid cysts in its epithelial investment (Fig. 28).

The abdominal and thoracic organs, liver, spleen, kidneys and lungs, are normal. The *ductless glands* show: Testes; complete degeneration of spermatogenous epithelium, no spermatozoa, increase in interstitial tissue, no Leydig's cells apparent. Thyroid: colloid goitre; no active hyperplasia. Thymus: no recognizable change. Adrenal: normal.

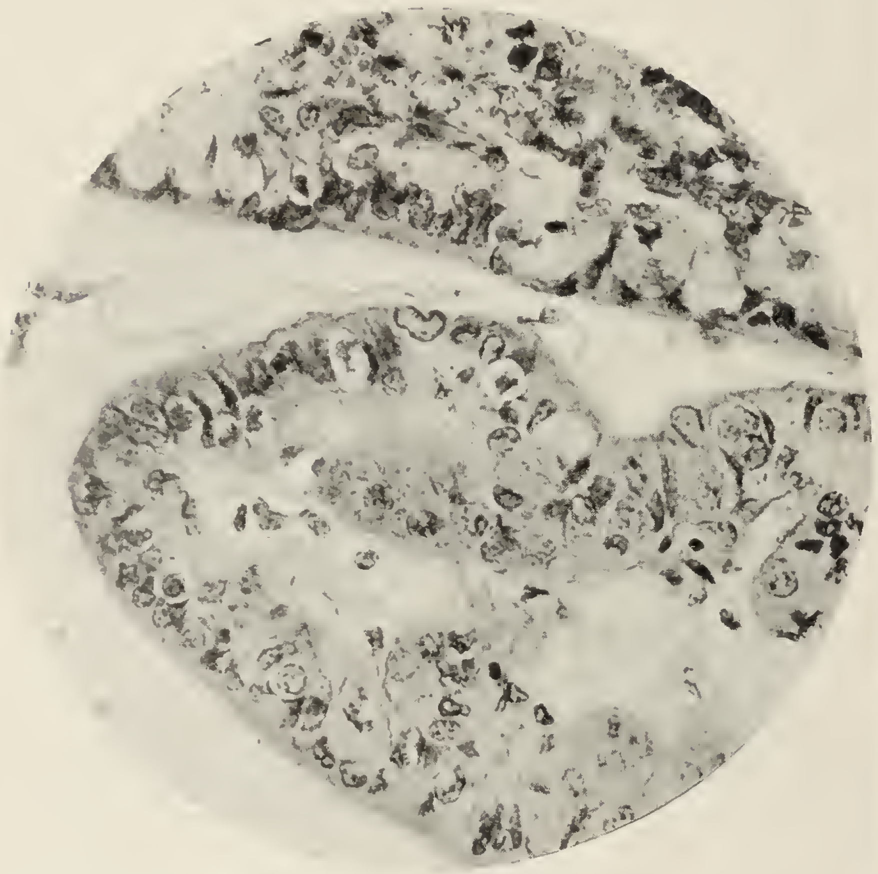

FIG. 27.—*Observation 33.* Activated cells of pars intermedia (hyperplasia?) after stalk separation.

The autopsy findings in this group are of especial interest, since they show that after separation from the base of the brain the structure, very much like a transplanted gland often degenerated, in large part, yet may retain enough viable cells to support life. It becomes reattached futhermore to the stump of the recently divided infundibulum and though slightly displaced from its former median position, as it was in all of our cases, it may nevertheless resume its normal function. The resultant condition, so far as the anterior lobe is concerned, is almost the same as if this portion of the gland had actually been removed and then reimplanted like a graft, for its circulation is almost entirely shut off.

The posterior lobe, on the other hand, though its blood supply should remain uninjured, nevertheless is seriously affected in another way; for, if we are to believe Herring's views, it discharges through the stalk and its secretion consequently will be dammed back by the resultant scar. In this connection the glandular blood supply and the presumed method of secretory discharge for the 2 portions of the gland deserve a brief description.

(a) *The Blood Supply of the Pituitary Body.*—Unreported studies made in this laboratory by Dr. G. J. Heuer and Mr. W. E. Dandy largely confirm, for the canine gland, the statements of Herring [31] in regard to its vascular supply in the cat. The arterial supply of the pars nervosa enters the posterior pole of the gland at the point of slight attachment encountered in the operation for removal. The anterior lobe, on the other hand, receives its supply from small vessels which pass down the infundibular stalk and break up abruptly into the large sinusoidal spaces characterizing the blood vessels of this portion of the gland. There seems to be no free anastomosis between these systems.

FIG. 28.—Pars nervosa of *Observation 33*, infiltrated with hyaline and containing colloid cysts after stalk separation. Anterior lobe remains normal. *A*, anterior lobe; *B*, posterior lobe; *S*, line of stalk separation.

Separation of the stalk consequently will shut off the direct blood supply to the pars anterior in many cases, almost as effectually as though the structure were actually taken from its bed. Thence arises the analogy between this operative measure and a favorable reimplantation elsewhere of this portion of the gland after its removal. Paulesco pointed out that in one of his cases at least, there was extensive degeneration of the pars anterior cells—just such a degeneration as we have

[31] P. T. Herring: The histological appearances of the mammalian pituitary body. *Quart. J. Exper. Physiol.*, 1908, II, 154.

seen in almost all of our transplants, and in one of these stalk separations (*Observation 20*) both lobes were almost completely degenerated, owing to accidental severance of the vessels to the posterior lobe when the stalk was being freed before its division.

That a large portion of the gland may retain its vitality, however, is evident from the condition found in *Observations 33* and *90* (Fig. 28); and in the protocol (*Observation 33*) just given, although it is probable, in view of the threatened cachexia hypophyscopriva symptoms, that the amount of functionating tissue was temporarily insufficient, nevertheless this period was tided over by injections. We shall see that it is possible to tide over a similar critical period after nearly total (anterior lobe) removals by glandular administration in one form or another.

(b) *The Question of Posterior Lobe Secretion.*—In describing the histological appearances of the posterior lobe in the cat, Herring calls attention to the peculiar faintly acid-staining "hyaline bodies" which are to be seen in the pars nervosa and appear to be making their way upward in the loose tissue channels toward the infundibulum. He came to believe that

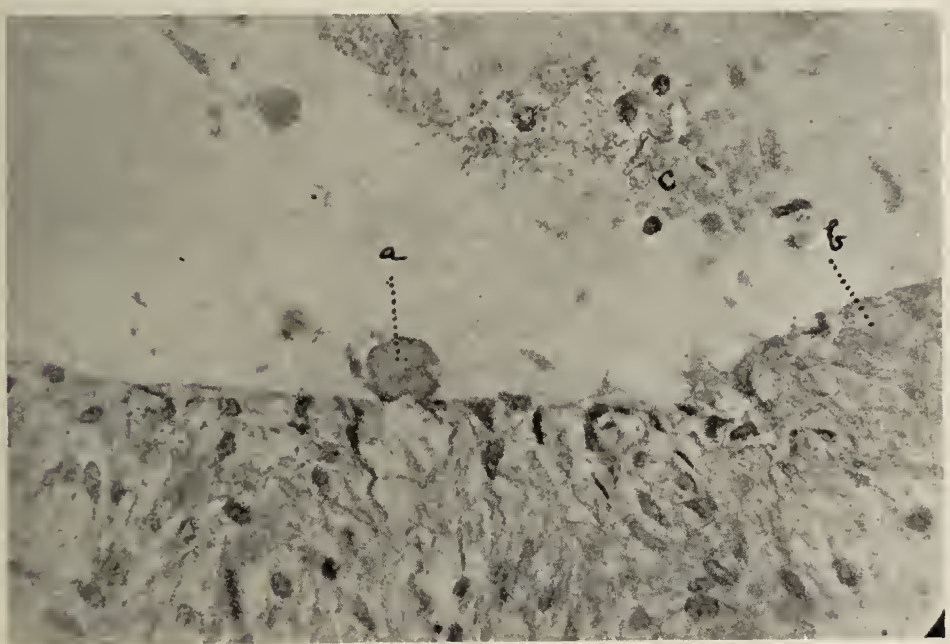

FIG. 29.—Hyaline bodies in *Observation 98* at infundibular floor; (*b*) before discharge, (*a*) after discharge. (Were it not a fairly common picture (*a*) might be considered an artefact.) (*c*) hyaline debris in ventricular cavity.

these bodies actually represent the secretion of this part of the gland, and they certainly occur in the situation in which the active principle has been demonstrated to lie.

The conditions are the same in the canine hypophysis, and we agree with him that the histological appearances point strongly toward the fact that this is an actual secretion and one which appears to be a product of activity of the cells of the epithelial investment (pars intermedia). The material seems to pass toward the infundibulum and in many cases may actually be seen passing into the cavity of the third ventricle (Fig. 29).

Certain of our surgical experiences, too, seem to lend direct support to Herring's hypothesis based on the study of normal tissues, and the more we have studied the posterior lobe in various post-operative conditions the more we have been inclined to accept his views. A great excess of the hyaline bodies is found in the tissues of many of our animals (Fig. 29a), and particularly in the stalk separations (as might be expected on the basis of this hypothesis) the pars nervosa may be crowded with them (Fig. 30).

It would appear that these hyaline globules take their origin from the cells of the pars nervosa, and indeed they actually resemble wandering cells, for in those bodies which lie nearer the epithelial investment ghosts of nuclei which apparently become extruded may often be made out (Fig. 31). In many conditions there seems to be an actual invasion of the pars nervosa by normal appearing cells, which gives an appearance akin to the tissue invasion by the cells of an epithelioma and one which is very often seen in the glands of adult man. Ordinarily, however, normally staining pars intermedia cells are not to be found far from the epithelial investment.

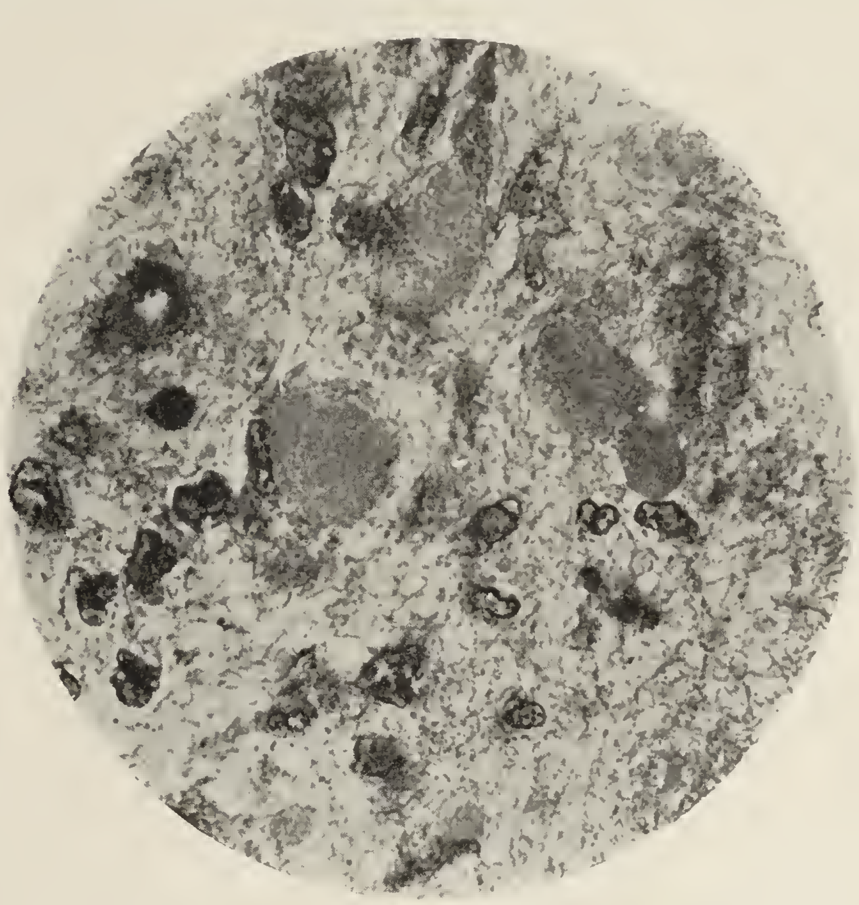

FIG. 29a.—Showing hyaline in pars nervosa of normal animal after glandular transplantation.

It was first pointed out by Howell that the blood pressure raising substance of the posterior lobe is limited to the pars nervosa, and we have failed to obtain any pressor response from injecting pars intermedia extract carefully prepared in the laboratory from the fresh glands of the pig. Neither does the true colloid secreted by the pars intermedia seem to contain the active principle, for the injection of the contents of large colloid cysts (bovine and human) has proved negative in our hands. It would seem probable, therefore, that the pars nervosa must in some way activate these hyaline bodies (at least if they are in any way related to the glandular colloid) during their passage toward the infundibular cavity.

These seem to be definite pathways for the "secretion" in the loose tissue spaces between the ependymal cell prolongations, and in cases of total or nearly total removal streaks of hyaline bodies are often seen passing through the nervous

tissue and extending from the remaining hyperplastic tags of pars intermedia up to the ventricle. Particularly after a stalk separation the posterior lobe may be found packed not only with colloid, but with these hyaline bodies as well (Fig. 28), and we are under the impression that the glands of individuals who have been afflicted with an obstructive hydrocephalus show much the same condition, and for the same reason—a matter to be considered on another occasion.

If these conjectures as to the secretory nature of the hyaline bodies, their origin from the pars intermedia, their activation during their passage through the pars nervosa, and their ultimate discharge into the cerebro-spinal fluid are to receive confirmation, they will represent a hitherto unrecognized form of glandular activity and a most bizarre outlet for its secretory products.[32]

The products of anterior lobe secretion, judging from the

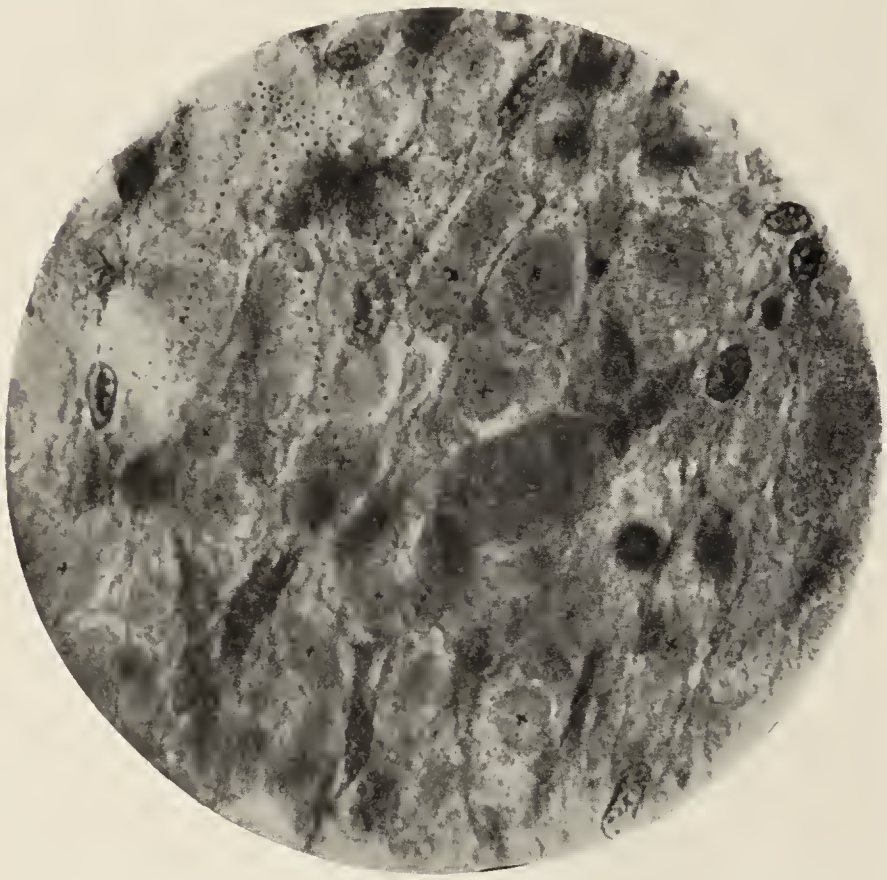

Fig. 30.—Showing channels in posterior lobe crowded with hyaline bodies (a few of them indicated by *x's*) after stalk separation.

topographical arrangement of the cells along the thin-walled blood sinuses, probably enter the blood stream directly, and in certain pathological states one may even find the peculiar anterior lobe colloid within the vessels themselves. Colloid, however, does not seem to be the normal form of pars anterior secretion, and pathologists are as yet undetermined as to whether there may not be various forms of cellular activity corresponding to the 3 types of cells, acidophiles, basophiles and neutrophiles. Certain observations of our own favor the view advanced by Erdheim, that each of the 3 types possesses a differing function rather than that each variety represents merely a differing stage of cellular activity.

[32] This is not, however, so bizarre when we realize how closely the cerebro-spinal space is connected with the blood stream; for the cerebro-spinal fluid, contrary to the usual interpretation of its function, seems to have a constant circulation and ready escape by way of the dural sinuses directly into the venous blood stream.

4. *Partial Removals of the Anterior Lobe.*—Hitherto, as has been pointed out, experimental removal of the hypophysis has had for its main object the determination of the essentiality or otherwise of the structure, and although opinions have differed, it is to be hoped that our confirmation of Paulesco's work will help to answer the question in the affirmative and show, at the same time, that it is the anterior lobe which is essential to life. Our predecessors in this work, however, have practically made either no comment (cf. *Table I*) on the late consequences of partial removal or else have denied (even after total removal) that any symptoms supervene.

One of the adult "partials" in Paulesco's series to which we have referred, lived for a year, became mangy, and died in a state of coma after "catching cold." This animal (*Expérience LXIII*), a male adult, gained in weight, as shown by the protocol, and had an occasional subnormal temperature. This

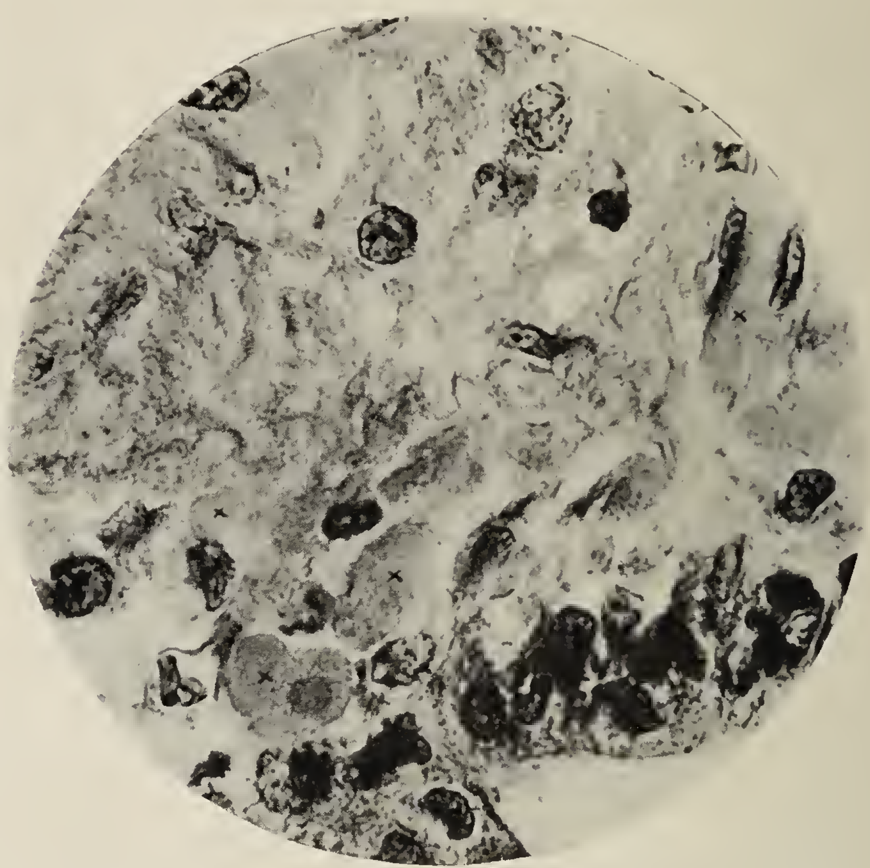

Fig. 31.—Showing edge of pars intermedia discharging hyaline bodies into pars nervosa (*x's*).

apparently was not regarded as an evidence of hypopituitarism, as Paulesco concludes:

> Aucun symptôme particulier et caractéristique ne traduit cette insuffisance relative du fonctionnement de l'organe pituitaire à la suite de l'hypophysectomie presque totale. L'animal se comporte absolument comme les animaux témoins, à hypophyse intacte..... Il est à noter que, chez les animaux dont la survie a été longue (5 mois, un an), aucune modification trophique appréciable n'est survenue au niveau des extrémités (museau, membres).

It was not until comparatively late in the course of the 1908-1909 series that our attention was called to peculiar and unmistakable alterations in some of the animals which had been kept under observation for weeks or months, a number of whom were even regarded surgically as presumptive "totals"—a fact which kept us long uncertain as to the actual essentiality of the gland, for the matter could not be settled for this particular group of cases until the final microscopic examinations were

made. Indeed, in one of the presumed totals (*Observation 98*) which was kept over until the present year, this final test of totality was only recently made, though our experience had made us sufficiently confident of finding a viable fragment in this, as we had in all other long-lived cases.

These unmistakable states of hypopituitarism to be described, we regard as far the most important outcome of our year's work, for they serve to throw light on the corresponding clinical conditions in man which have just begun to receive attention through the articles of Fröhlich, Frankl-Hochwart, Brissaud and others, but which could not have been suspected as being due to glandular inactivity of the pars anterior without these suggestive experimental states.

To throw further light on this aspect of experimental hypophysectomy has been the chief object of the 1909-1910 experiments still in progress under the direction of Dr. Goetsch and it must suffice for this present report to recount our preliminary observations.

The following tables include 18 partial hypophysectomies, in 6 of which a part of the anterior lobe alone was removed, leaving the posterior lobe *in situ* (*Table VII*), whereas in the remaining 12 observations the pars nervosa, with its investment, was included in the partial extirpation (*Table VIII*). Although there was no striking difference in the post-operative symptoms shown by the individuals in these 2 groups, they are presented, nevertheless, in separate tables for the purpose of further emphasizing the physiological importance of the pars anterior, for the results seem to be practically the same with or without removal of the posterior lobe. This might have been expected could we have foretold (1) that a *complete* extirpation of the anterior lobe would be invariably fatal, even when the posterior lobe and its epithelial investment are left intact, and (2) that the posterior lobe alone could be removed and the animal survive for an indefinite period.

(a) *Effects of Partial Removal of the Pars Anterior, Leaving the Posterior Lobe in Situ* (*Table VII*).—The operations in 3 (*Observations 29, 30, 31*) of these 6 animals were intended for adult total anterior lobe extirpations, but the unexpectedly long survivals, averaging 28 days, were accounted for by the post-mortem demonstration of viable, though microscopic anterior lobe fragments embedded in the scar-tissue. These may be compared with *Observations 61* and *66* of *Table VIII*, cases in which the posterior lobe was removed as well, the terminal symptoms not occurring until 60 and 37 days after the operation, a longer survival than in the fatal cases with retained posterior lobe.

The duration of life in the cases retaining these minute fragments, is proportionate according to Paulesco to the size of the fragment, but it would seem better to say that it is proportionate to its cellular activity rather than to its mere size. Favorable external circumstances, furthermore, are important, for accidental infections, exposure, digestive disturbances and what not may doubtless prove the determining element of sufficiency for in their absence an astonishingly minute fragment may serve the animal's physiological needs.

Of the other 3 cases of *Table VII*, *Observation 26* succumbed within the usual time to symptoms of cachexia hypophyseopriva, despite the retention of a minute anterior lobe fragment which, however, was found much lacerated and infiltrated with blood. *Observation 34* lived for many months, as did also *Observation 27*, the latter case being complicated somewhat by an associated thyroidectomy performed in the hope of accentuating the histological changes of the remaining fragment. Owing to this some of the symptoms suggestive of hypopituitarism—the gain in weight, thickness of skin, hypotrichosis and subnormal temperature—might have been ascribed to myxœdema. The microscopic studies of the fragment of *Observation 27* showed it to be small and completely enveloped in scar-tissue, but the individual cells were much enlarged, containing huge vesicular nuclei and an abundant protoplasm showing but few faintly staining eosinophilic granules—an appearance which we have come to regard as representing active hyperplasia (cf. Fig. 36). The posterior lobe was shrunken and almost entirely replaced with ingrowths of pars intermedia cells with an abundance of colloid and many hyaline bodies, comparable to the condition described in *Observation 33* (Figs. 27 and 28), a case of stalk separation. The ovaries were small and sclerotic and contained very few developing ovules.

Inasmuch as *Observation 34* was the first of the experiments in which the excessive adiposity was noted and as no attempt was made to modify the progress of the symptoms until the injections were made at the end of 6 months, the case deserves to be recorded in greater detail. An abstract of the protocol follows:[33]

Observation 34. *Partial removal of anterior lobe with stalk separation; symptoms of hypopituitarism, adiposity, etc.; febrile reaction to injection of anterior lobe extract; sacrificed after 6 months.*

Adult female 14-pound fox-terrier.

December 18, 1908. Operation: Partial removal of anterior lobe; posterior lobe *in situ* though stalk separated. No operative complication and prompt recovery from anæsthetic.

December 19. Bright though inactive and very irritable. Takes milk and water. Urine 1200 cc., no sugar.

December 24. There have been no post-operative complications; wound has healed *per primam*. Animal taking solid food. Urine 1340 cc.

January 24, 1909. Has gained 3¼ pounds during the past month. *Weight* 17½ pounds (Fig. 32). Polyuria has persisted, varying between 980 and 1320 cc. Temperature occasionally slightly subnormal.

February 15. Though rather inactive the animal has shown a good appetite for the past 3 weeks. There has been considerable shedding of hair, but her coat is not rough and bristly as in some other of the more completely hypophysectomized animals. With the exception of the persisting polyuria, nothing unusual has been observed. Urine to-day 1260 cc., no sugar.

March 4. Weight 19½ pounds. Very sleek and fat, though fed on usual rations with control of same age. Appetite does not seem excessive.

March 22. Weight 22 pounds, a gain of 2½ in 18 days (Fig. 33). Urine 920 cc. Animal continues sleepy, dull and inactive. Temperature often slightly subnormal.

[33] This case is also recorded in full in Ziegler's Beiträge.

May 10. Since the last note has been allowed the freedom of the paddock with other animals. She has apparently not been in heat since the operation. Polyuria persists; urine to-day 1440 cc., no sugar. She is sleek, fat and inactive. *Weight 23 pounds.*

May 20. Replaced in metabolism case for the past 10 days; polyuria even more marked than heretofore, averaging 1620 cc.

May 28. Animal continues in cage. Appetite is fair, but she is not ravenous, as food is often left in her pan. She is inactive and sleeps much of the time. Temperature 36.5° C. (the first marked subnormal registration); pulse 128. Urine 980 cc., no sugar. Her *weight* to-day is 23¾ pounds, while that of a control bitch who has been kept under like conditions is only 16 pounds (Fig. 34).

June 14. Since the last note animal again turned in yard. There has been no sign of her being in heat. Polyuria persists. Urine 1140 cc., no sugar. *The total gain in weight has been 9¾ pounds—over 70 per cent increase.*

At this juncture, with temperature 38° C., pulse 136 and urinary output 880 cc., a subcutaneous injection of 10 cc. of boiled anterior

Fig. 32.—*Observation 34.* Adult fox terrier bitch. Photograph 36 days after operation, when striking gain in weight first began to be observed.

lobe aqueous suspension (ox)[34] was administered, leading to a marked febrile response to 40.6° C., and to an increase in polyuria, namely, 2400 in 24 hours. The pyrexia continued for three days with no local reaction at point of injection, and at the end of this time the animal was sacrificed.

June 17. Autopsy: The panniculus over chest and abdomen varies from 5 to 8 cm. in thickness: there is an especially marked accumulation of fat around the lower jaw and back of the neck. No local tissue reaction at site of injection.

Mammary glands and *nipples* are small and undeveloped.

Paws are small and free from fat. There are no apparent abnormalities in the long bones (no sections).

Head: The operative wound has healed perfectly. Brain and meninges appear normal. The remainder of the hypophysis is more firmly adherent than normal to the infundibular region and a considerable fragment of the anterior lobe is recognizable by its color.

Neck: Thyroids are firm, colloidal and slightly larger than normal; parathyroids prominent. No definite traces of thymus are seen.

Thorax: Lungs and pleura are normal.

Abdomen: Intestines and peritoneum are normal. The *liver* is obviously fatty, looking almost white on gross section.

Kidneys, pancreas and *adrenals* show no gross abnormalities.

Ovaries are small and buried in fat.

Uterus is infantile and is represented by a mere thread of tissue (hypoplasia).

Microscopic. *Base of Brain:* Serial sections through the infundibular region and hypophysis show that the gland, whose stalk was purposely separated at the operation, has become reunited to the base of the third ventricle in nearly normal position. The *posterior lobe* is markedly altered. There is no trace of the original *pars nervosa,* the entire lobe being filled with pars intermedia cells, many of them forming acini containing colloid, so that the condition resembles active thyroid tissue. The appearances are interpreted as due to stasis of posterior lobe secretion. A considerable fragment of the *anterior lobe* remains; it is very vascular, the blood sinuses being greatly dilated. The cell columns show many brightly-staining, small eosinophiles which line the blood vessels. The centers of some of the cell columns contain groups of nuclei with scant protoplasm which takes no stain (Kernhaufen of Rogowitsch).

Fig. 33.—*Observation 34.* Ninety-two days after operation. Condition of adiposity well established. Note disproportionately small and delicate extremities.

Thyroid: Cells flat; acini distended with colloid.

Liver: Diffuse and marked fatty degeneration of all cells. *Myocardium* also shows fatty change.

Pancreas and *spleen* appear normal.

Adrenal: Marked vacuolization of cells of deeper layer of zona fasiculata.

Ovaries: Many developing ova which appear normal: 3 large irregular shaped areas made up of vacuolated chromaffine cells (abnormal corpora lutea?).

This was the first case in which we observed the symptoms which characterize certain tumors of the hypophysis of the type described by Fröhlich, a physiological explanation for which on the grounds of glandular deficiency has heretofore been impossible. The more noticeable alterations from the normal were the marked adiposity, abeyance of the sexual function, polyuria, sleepiness, and the tendency toward a subnormal

[34] Prepared by dissolving 1 gram of the dried powder of the anterior lobe of the ox in 100 cc. of distilled water, boiled.

temperature. Possibly the *most important incident of this history, however, was the thermic response to the injection of anterior lobe extract*—a part of the gland which under normal circumstances has long been known to give no reaction.

(b) *Partial Removal of the Pars Anterior Together with the Entire Posterior Lobe* (*Table VIII*).—This group includes 13 cases in which the posterior, as well as the greater portion of the anterior lobe, was removed. A number of them were considered to be "totals" at the time of operation. Three of the cases succumbed to cachexia hypophyseopriva. Of these, *Observation 43*, an adult, died on the 2d day. The minute fragment, though showing normal staining reactions, was found infiltrated with blood, and had the operation not been conducted in the winter months or had a timely injection or a transplant been used, recovery would have been possible.

Observations 61 and *66* were puppies, also surgically regarded

Fig. 34.—*Observation 34* (right), 153 days after operation, weight 23¾ pounds, a gain of 9¾ pounds. Control (left) kept under like conditions weighs 16 pounds.

as totals. The former, aside from a transient polyuria, remained well and gained in weight until on the 54th day it caught distemper, became somewhat lethargic, and with a fall in body temperature gradual symptoms of cachexia set in (Fig. 35) which led to death in 6 days. The clinical course of *Observation 66*, barring the infection, was in many respects similar. The animal was bright and lively for 2 weeks and gained 2¼ pounds in this interval. The onset of the terminal symptoms was most gradual, though characteristic in all features, and it was 24 days before death occurred, the body temperature having fallen to 17.5° C. before the end. In both of these cases a microscopic viable anterior lobe fragment was found (Fig. 36), and though insufficient to support life, nevertheless it can be seen that the usually abrupt terminal symptoms characterizing the "totals" were much prolonged.

In 3 of the other 9 cases, *Observations 49, 88* and *100*, the remaining fragments were likewise microscopic and their identification necessitated a careful search through the serial sections. The animals all showed temporary symptoms of postoperative cachexia, *Observation 100* being sacrificed while they were in evidence, for examination of the tissues. The other 2 recovered. One of them (*88*) was in good condition when sacrificed on the 12th day, and microscopic examination revealed a small fragment of anterior lobe surrounded by an organizing blood-clot. The anterior lobe cells were of the actively secreting type (Fig. 37), and it is a natural conjecture that the fragment was so damaged that for a few days after the operation it was functionally insufficient, but owing to restoration of its activity with hyperplasia, complete recovery of the animal followed. Analogous recoveries after the development of hypophyseopriva symptoms have been seen, as we have stated, after total hypophysectomies with immediate cortical implantation of the recently removed gland; and the histologic appearance of the transplants, in these cases also,

Fig. 35.—*Observation 61.* Presumed "total"; proven "partial." Photograph 52 days after operation. Note characteristic posture of early stage of cachexia hypophyseopriva precipitated by attack of distemper.

suggested an extreme degree of activity on the part of the cells of the anterior lobe.

Observation 49 is in many respects similar to the above case. Apparently the entire gland was removed at operation, and for the succeeding 2 or 3 days the animal was lethargic, refused food and had a subnormal temperature. On the 4th day, however, the normal conditions became restored and the animal was sacrificed 17 days later. A microscopic fragment of anterior lobe was found with its cells almost identical in appearance with those of *Observation 88*. The thyroids presented definite hypertrophic changes, possibly compensatory ones since corresponding changes are said to occur in the pituitary body after primary removal of the thyroids. A further description of the

histological alterations of the pars anterior denoting what we regard as hyperplasia, must be deferred for a subsequent communication.

Fairly good fragments were present in *Observations 71, 80* (Fig. 8) and *81*. These 3 animals were sacrificed for tissue study after some weeks had elapsed, but before definite symptoms of chronic hypopituitarism had occurred, though they were gaining in weight.

Observation 81, a small female (Figs. 7 and 38), showed a gain of 2 pounds in the 34 days. These symptoms, however, were much more definite in the 3 animals (*Observations 54, 55* and *98*) allowed to survive a longer time. In *Observations 54* and *55* the fragments were large enough to be seen by the naked eye, whereas in *98* it was of microscopic size and the animal did not become fat.

Fig. 36.—*Observation 66* (*Table VIII*). Showing fragment of anterior lobe left after an hypophysectomy supposedly total. Fragment in active hyperplasia.

Observations 54 and *55* are of especial interest, for, though adult males, they present many clinical similarities to *Observation 34* (*Table VII*) and are a striking illustration of a moderate degree of chronic hypopituitarism. *Observation 54* (Fig. 39) was an adult, mongrel, 16-pound, black spaniel, with possibly three-fourths of the anterior lobe removed. A post-operative polyuria appeared and persisted and in this case a transient glycosuria was observed (estimated from polariscopic readings at 1.65 grams of glucose to the liter). The animal gained from 16 to 27 pounds in the 3 months following the operation, became sexually impotent (or indifferent), had an occasional subnormal temperature, and gave a definite thermic response (from 38.6° C. to 41.8° C.) as well as blood pressure and respiratory ones to the intravenous injection of 3 cc. of the standard 1 per cent aqueous solution of anterior lobe extract.

The symptoms in *Observation 55* were exactly the same but with a more persistently subnormal temperature, often as low as 37° C. even during warm weather (June), and a marked thermic response from 38° to 42.5° C. in 2 hours after the test anterior lobe injection. It was in this case that the post-operative testicular atrophy (Figs. 40 and 41) was for the first time strikingly called to our attention. The protocol follows:

Observation 55. *Partial hypophysectomy; transient polyuria; atrophied genitalia; impotency* (?); *adiposity; sacrificed 104 days after operation.*

Adult male fox-terrier, 2 years of age, weighing 17 pounds.

March 3, 1909. Operation: Supposedly a total removal. No post-operative complications.

March 4. Animal active and seems brighter than is usual for an adult animal the day after a total hypophysectomy; drinks water and milk greedily. Temperature 38.5° C.; pulse 165, irregular. Urine for 24 hours preceding operation 200 cc. (no sugar); for 24 hours following, 1100 cc. (no sugar).

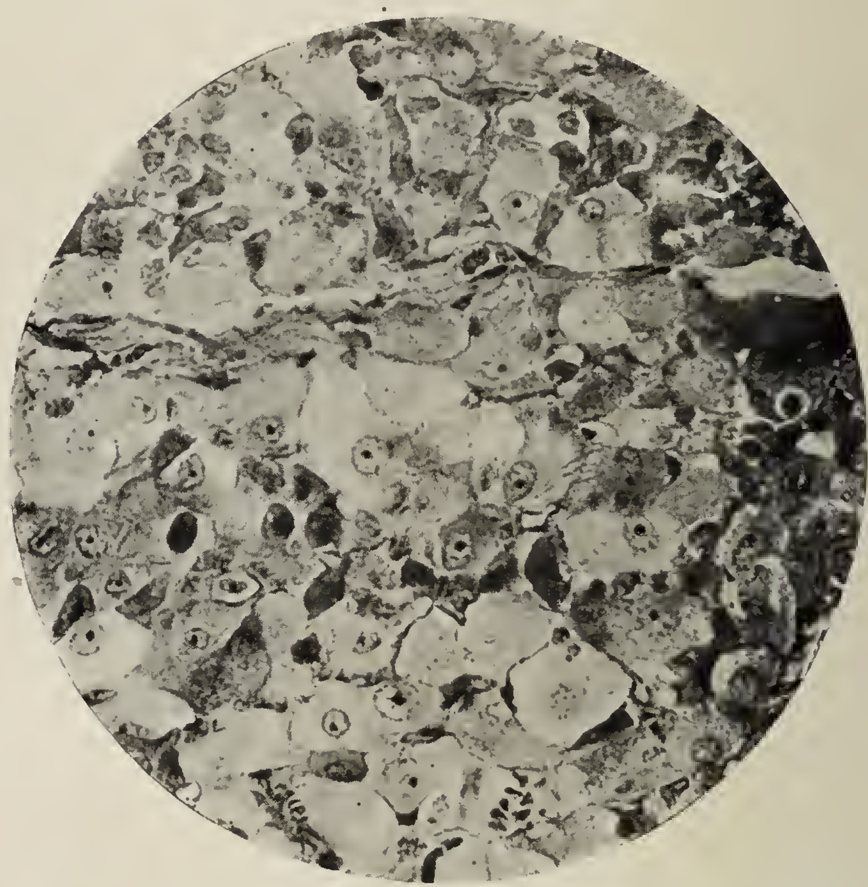

Fig. 37.—Showing character of change (hyperplasia?) seen in many anterior lobe fragments. Dark staining acidophiles, few in number; most of the cells being enormously enlarged and staining indifferently.

March 5. Urine 870 cc., no sugar.

March 6. Wound healing perfectly. Animal has shown no symptoms of cachexia hypophyseopriva. Appetite continues good. Temperature 38.5° C.; pulse 76, very irregular. Urine 230 cc., no sugar.

March 7 to 16. Continues in very good condition; eats well; weight 18½ pounds. Temperature 38.4° C.; pulse 88, irregular. Urine 320 cc., no sugar.

April 10. In very good condition. Temperature 37.8° C. (slightly subnormal); pulse 98, regular. Urine 400 cc., no sugar.

May 1. Weight 21½ pounds—a gain of 4.5 pounds since operation. Bright and lively. Temperature 38.4° C.; pulse 88. Urine 360 cc.

May 1 to June 4. During this period has been allowed freedom of paddock with other animals. Does not seem sexually normal (will take no notice of a bitch in heat when placed with her). Hypoplasia of the external genitalia has become obvious (Fig. 40).

June 5. Temperature 37.9° C.; pulse 76. Urine 770 cc. (slight polyuria again).

June 12. Polyuria continues; urine 840 cc., no sugar. Seems to be sexually impotent. Temperature 38.2° C.; pulse 92, irregular.

June 15. Bright and playful. *Weight* 23 pounds—a gain of 6 pounds since the operation (Fig. 41). Temperature 38.4° C.; pulse 92. Urine 800 cc., no sugar.

On this date an *injection* of 3 cc. 1 per cent solution of anterior lobe (ox) was given intravenously to investigate the thermic blood pressure and respiratory reactions under these conditions of hypopituitarism. Immediately following the injection there was a slight rise in blood pressure (as was seen in 4 other instances of a similar anterior lobe injection in animals with a partial removal) and a marked respiratory attack (respiration from 40 before to 300 after injection). *Two hours* after injection the animal's temperature had risen to 42.5° C., being 3.8° C. above the normal.

Animal was sacrificed 3 hours after the injection.

Autopsy: Body unusually fat. Panniculus measures from 4 to 5 cm. in thickness over chest and abdomen. Crainal wound healed perfectly. Brain and meninges normal. To the naked eye there is a small tag of tissue in the hypophyseal region which presumably contains an interior lobe fragment.

Testes firmer than usual and less than half normal size. Other organs appear normal.

Microscopic: In the hypophyseal region there is a strip of active pars intermedia cells, a portion of the cleft and a small fragment of anterior lobe apparently in hyperplasia: also an appearance in the ventricular wall suggestive of ependymal hypertrophy. The glandular fragment is embedded in scar-tissue which has undergone a peculiar fatty change.

Fig. 38.—*Observation 81.* Adult multipara. Nearly total removal. Photograph 10 days after operation. Gaining in weight.

Testes: Complete degeneration of spermatogenous cells: no spermatozoa. *Adrenals:* Extreme vacuolization of cells in lower layer of zona reticularis; hyperplasia (?) of medulla. *Thyroid:* Acini distended with excess colloid; lining cells flat. Liver, kidneys and other organs practically normal.

These cases, *Observations 54* and *55*, together with *Observation 34* (*Table VII*), are the most representative illustrations in our 1908-1909 series of the effects of long-enduring hypophyseal deficiency of moderate degree. Further advances in this direction have been made in the 1909-1910 series, but as studies of this kind necessarily cover many months, the report of these more complete observations must be deferred until all the tissues can be obtained and thoroughly studied.

Owing to the long survival a final case from *Table VIII* deserves mention.

This animal (*Observation 98*), a young black and tan bitch, surgically a presumed " total " was kept under observation for 9 months —the only one of our series allowed to survive for this length of time. She recovered promptly from the operation (June 11, 1909) and showed the usual polyuria but no symptoms of cachexia hypophyseopriva during the unfortunately short period of observation before the summer vacation.

In October she was found with a thick, dry skin and hypotricosis, and though not noticeably fat she had gained considerably in weight. Up to March, 1910, when sacrificed, she apparently had never been in heat. Her carbohydrate tolerance was estimated (70 grams cane sugar) and an anterior lobe injection test was made, the temperature rising from 38.8° to 40° C. in 2 hours, with the usual gradual return to normal. A control animal gave no thermic response.

Fig. 39.—*Observation 54.* Two months after partial hypophysectomy. Animal dull, sleepy, impotent, with 10-pound gain in weight.

At *autopsy* a microscopic fragment of anterior lobe was found (Fig. 42); the thyroids were colloid in character, suggesting former hypoplasia (Marine); the infantile uterus was represented by mere threads of tissue and the ovaries were entirely undeveloped.

5. *Hypopituitarism.*—Just as in cretinism *versus* myxœdema and gigantism *versus* acromegaly—states which differ only in so far as the process has originated either before or after adolescence, so apparently may we have 2 types of hypopituitarism. The adult animals become adipose and sexually degenerate, whereas the young likewise often grow fat but they remain undersized (as Fichera found to be the case with chickens), and sexual infantilism persists. Polyuria, glycosuria, a slightly subnormal temperature, changes in the nutritional condition of the skin and its appendages, with hypotricosis and occasional

FIG. 40.—*Observation 55.* Two months after partial hypophysectomy, when genital hypoplasia first became apparent. Gain of 4 pounds in weight (cf. Fig. 41.)

FIG. 41.—*Observation 55* (left), 3 months after operation, showing gain of 6 pounds and extreme genital atrophy; (right) normal control of same age.

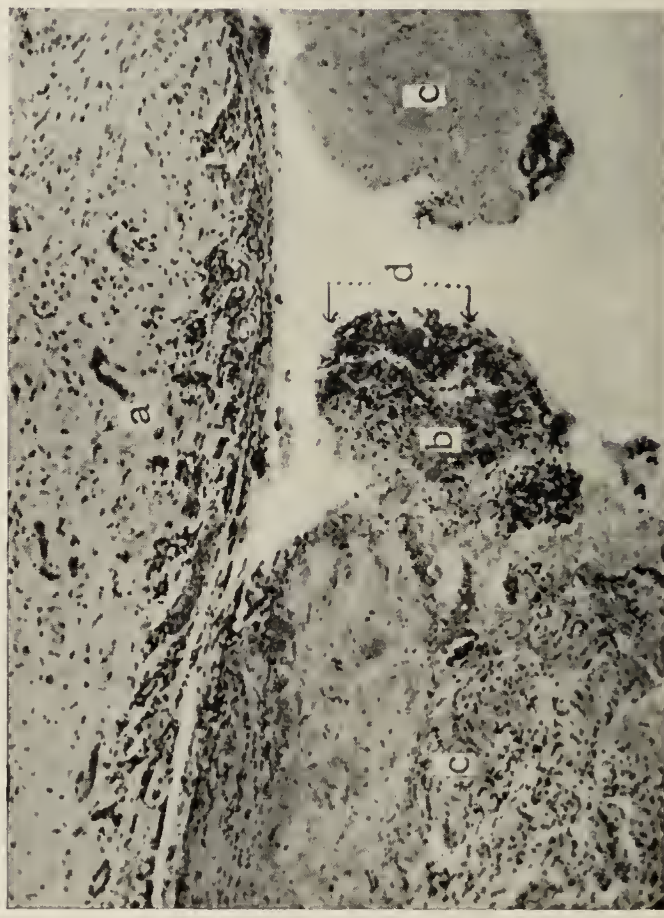

FIG. 42.—Microscopic pars anterior fragment from *Observation 98 (Table VIII)*. *a*, infundibular wall with few pars intermedia cells; *b*, chiefly pars intermedia cells; *cc*, cicatricial tissue; *d*, fragment of pars anterior.

FIG. 43.—Showing (right) a puppy's liver mottled by extensive focal necroses after 13 consecutive subcutaneous injections (each representing the emulsion of a single entire canine gland) contrasted with normal liver of control puppy (left) from same litter.

transient œdemas, are usual symptoms. Psychic disturbances have been common, sometimes with inactivity and sleepiness, sometimes the reverse with a restless playfulness. Many of the animals are more irritable than normal.

Further data in regard to these matters must be kept for our 1909-1910 reports, which will not only more clearly show the effect of the partial hypophysectomy upon growth, but will also throw further light on the histological alterations in the other ductless glands, of which we had only begun to have glimmerings, restricted largely to the occasional acute thyroid hyperplasia after total removal, and the atrophy of the spermatogenons epithelium in the long-lived adult males.

6. *Transplantations and Injections Associated with Partial Removals.*—We have mentioned in an earlier section the fact of having made 23 experiments with glandular grafts in the hope of setting aside or modifying the symptoms of cachexia, which are inevitable after total removal of the gland. Only 7 of the hypophysectomies, however, in which the transplants were made, were subsequently proven to be "totals," minute anterior lobe fragments having been found at the base in all of the other 16 cases. Many of the remaining 16 animals showed transient post operative symptoms of cachexia from which the majority recovered, and almost all of them were sacrificed after 2 or 3 weeks—too early for definite signs of hypopituitarism to have manifested themselves—for the purpose of studying the condition of the transplanted tissue.

The grafts in most instances showed a peripheral zone containing viable cells, but as their centers were always entirely degenerated we placed little trust in the functional capabilities of the comparatively small normal residue for at the time of making these grafting experiments we were unaware that a microscopic fragment might support life if the early symptoms could be tided over, as doubtless they were in many instances by these transplants. In one of the puppies, indeed, a secondary wave of cachexia hypophyseopriva symptoms appeared a month after the hypophysectomy, at which time the removed tissue had been implanted under the rectus muscle: a second (homogeneous) gland was immediately ingrafted, with prompt improvement in the symptoms and ultimate recovery. Doubtless, in view of our experiences with the 1909-1910 series, subcutaneous injections of the boiled emulsion of the anterior lobe would have answered the same purpose.

Among the *Observations* not included in the 8 tables which accompany this paper, the purely surgical results were confused in many instances by *injection experiments* with the extract or emulsion of one or another subdivision of the hypophysis prepared by ourselves either from the aseptically removed canine gland, or from fresh glands of the pig or ox secured from the abattoir.[35] It was found that a suspension of the powdered posterior lobe does not lose its activity on boiling, and apparently the same is true of the pars anterior as well, if we can rely on the thermic reaction (cf. below) as a test. An aqueous suspension of the dried and powdered gland can therefore be sterilized before injection.

To briefly summarize our experiences: Repeated injections of the entire gland, in the attempt to reproduce hyperpituitarism, was soon found to cause rapid loss of weight both in puppies and adults; and it was learned that this nutritional disturbance was due to the inclusion of posterior lobe in the preparations. It was in these animals that we first met with the extreme degrees of hepatic degeneration subsequently found under other of the experimental conditions. The external appearance of one of these mottled livers when contrasted with the normal, shows how extreme the degeneration may be (Fig. 43). This same lesion, is must be added, with no accompanying histologic change in the kidneys, has been found in a number of our hypophysectomized animals without injections. It

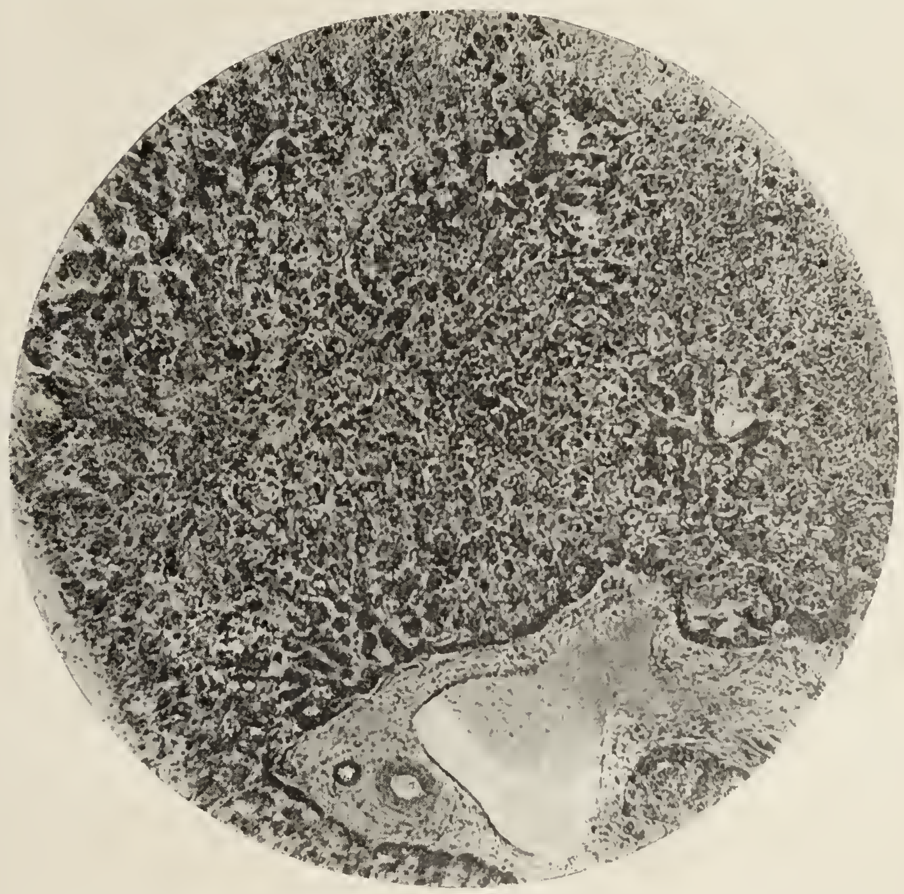

Fig. 44.—Showing extensive liver necrosis after whole gland injections × 60 diams. (cf. Fig. 43).

appears to be a form of extensive central?) necrosis (?) (Fig. 44).

The subcutaneous administration of pure anterior lobe preparations, on the other hand, caused no such disturbances, and in 1 instance a normal puppy was given daily injections over a period of 3 months without apparent ill (or other) effect. We consequently limited ourselves to the extract of pars anterior, not only for the attempted reproduction of hyperpituitarism, but also, and with evident success, as a therapeutic measure in substitution for the more elaborate transplantation procedure as a means of tiding over periods of threatened cachexia hypophyseopriva in the cases of "almost total" hypophysectomy. It was in the course of these undertakings that we first observed:

7. *The Thermic Reaction.*—Next to the experimental demonstrations of a recognizable symptomatology for states of hy-

[35] Mr. F. M. Bell, of the Armour Company, has kindly supplied us from time to time with large quantities of fresh bovine glands, and this company has now put upon the market the dried extract of both anterior and posterior lobes separately.

popituitarism, possibly the most important thing which we have stumbled upon during our studies of these animals is the occurrence of a thermic response to injections of boiled aqueous emulsion of the pars anterior in cases of anterior lobe deficiency (cf. protocols of *Observations 33* (*Table VI*), *34* (*Table VII*), *54*, *55* and *98* (*Table VIII*). This has been repeated without failure in practically all of the later anterior lobe "partials" of our own as well as in those of Dr. Goetsch's series; and judging from a few cases of suspected hypopituitarism in man, it appears to hold true for the human as well—a matter which may prove to be of value for the diagnosis of clinical cases. Needless to say, the reactions were controlled, with negative results, by posterior lobe injections in the partially hypophysectomized animals, as well as by injections of the emulsion of one or the other lobe in normal individuals.

The results given in this paper represent merely a stage in our investigations, and necessarily many suggestive topics have been merely touched upon. Further data in regard to the injection experiments as well as to those with glandular feeding, and a more detailed discussion not only of the histologic appearances of activation in the cells constituting the retained fragments, but also of the post operative alterations in the other ductless glands, must be left for the confirmation and additions of the 1909-1910 experiences.

VI. Summary.

Past investigations have led to no unanimity of opinion in regard to the physiological essentiality of the hypophysis cerebri. Thus, of the two most important studies those of Paulesco favor, while those of Gemelli oppose, the view that loss of the gland is necessarily fatal.

Accurate and uncomplicated removal of the gland from the dog—the animal most suited to these investigations—was impossible before the introduction of Paulesco's subtemporal procedure with its principle of cerebral dislocation, and many of the symptoms described by authors before him must in large part have been due to operative trauma, or, in the absence of symptoms, to incompleteness of removal.

We find, in agreement with Paulesco, that a state of apituitarism due to the total removal of the hypophysis leads inevitably to the death of the animal, with a peculiar and characteristic train of symptoms (cachexia hypophyseopriva). That these symptoms are not due to surgical trauma or post-operative complications is evidenced by the facts (1) that the same operative manipulations leaving the hypophysis in place and omitting the single step of removal leads to no symptoms whatsoever, and (2) that incomplete removals produce no immediate disturbances.

However, even in the case of adult animals death need not occur after a total removal as promptly as Paulesco claimed; whereas puppies may remain in an apparently normal condition for at least 3 weeks before the terminal phenomena appear.

These same symptoms, after the same intervals of time, follow the removal of the entire pars anterior alone, even though the posterior lobe remains in place. On the other hand, removal of the posterior lobe (necessarily leaving a small amount of pars intermedia) not only leads to none of the manifestations of cachexia hypophyseopriva, but does not appear to affect the physiological balance of the animal in any symptomatic way, unless the convulsions and excessive sexual activity which have been seen in a few cases can possibly be ascribed to its absence.

Separation of the hypophyseal stalk, owing to circulatory disturbances is comparable either to a partial hypophysectomy or to a total removal with immediate reimplantation of the excised tissue elsewhere in the body. The gland becomes reattached and the pathways for posterior lobe secretion (supposed to traverse the pars nervosa on its way to the infundibular cavity) may become obstructed by the scar, leading to an accumulation of "hyaline" within the channels of the pars nervosa.

Definite constitutional disturbances which we may regard as manifestations of hypopituitarism have been observed after partial (anterior lobe) removals in a number of animals kept under observation for long periods of time. The most striking feature is a state of adiposity accompanied by (or resultant to?) a secondary hypoplasia of the organs of generation in adults or by a persistence of sexual infantilism in case the primary hypophyseal deficiency antedates adolescence. Polyuria, glycosuria, alterations in the skin and its appendages, (such as œdemas and hypotrichosis) the tendency to a subnormal body temperature, and psychic disturbances are more or less frequent accompaniments—all of them symptoms which occasionally occur with states of adiposity and of sexual infantilism in man, in company with certain pituitary body tumors—states, therefore, which presumably are due to hypophyseal (anterior lobe) deficiency.

Animals, in states of hypopituitarism, appear to have a lowered resistance to infection, exposure or disease, conditions which are apt to precipitate the onset of cachexia hypophyseopriva.

It has been possible, by glandular transplantations or by injections of anterior lobe emulsion, definitely to prolong the life of animals after total hypophysectomy, and likewise to tide over periods of threatened cachexia hypophyseopriva in animals retaining anterior lobe fragments which temporarily may be physiologically insufficient.

Boiled anterior lobe emulsions appear to elicit a characteristic (anaphylactic?) febrile response when injected subcutaneously in states of experimental hypopituitarism.

TABLE II.—ADULT TOTAL HYPOPHYSECTOMIES.

Case number and operation.	Date.	Temperature.	Pulse.	Urine.	Sugar.	Clinical symptoms.	Duration of life.	Post-mortem conditions.
Observation 6.—Oct. 3, 1908. Fox terrier; male; complete removal in fragments; injury to temporal lobe.	October 4. October 5. October 6. October 7. October 8.	38.4° C. 38.2 38.2 38.2 30.1	168 144 120 124 120	....	....	Rotary progression (due to unilateral injury of the pyramidal tract); lethargy; arching of back; general muscular tremors; became comatose on 5th day after usual symptoms.	5 days.	Wound healed per primam; under surface of left temporal lobe lacerated and hæmorrhagic. Interpeduncular region occupied by a blood-clot; no evident remains of the hypophysis. Thoracic and abdominal organs appear normal. *Microscopical.*—A few pars intermedia cells remain; no trace of anterior or posterior lobes; organizing blood-clot.
Observation 12.—Oct. 29, 1908. Dry, clean exposure; no bleeding; entire gland removed in one piece; no injury to temporal lobe.	October 30.	28.0	Not palpable; heart-rate 40 to minute; very irregular.	Anuria.	....	Animal never entirely recovered from the anæsthetic; gradually became comatose after usual symptoms.	36 hours.	Brain and meninges appear normal; very small blood-clot at base; no evidence of anterior or posterior lobe. Lungs normal; abdominal organs appear normal. *Microscopical.*—A few pars intermedia cells remain; infiltrated with blood and leucocytes. No anterior-lobe cells seen (serial sections).
Observation 14.—Nov. 2, 1908. Dry, clean approach; gland removed in one piece; no hæmorrhage; floor of 3d ventricle torn out, with escape of cerebro-spinal fluid.	November 3. November 4. November 5. November 6.	35.0 33.8 33.2 26.0	120 116 120 Not palpable.	120 cc. 60 80 Anuria.	....	Promptly recovered from anæsthetic; on following day was lethargic; if aroused will walk unsteadily around the room; arching of back; comatose on 3d day; temperature subnormal; reflexes retained; pulse feeble and irregular.	4 days.	Base clean, no blood-clot. Areas of bronchial pneumonia; abdominal organs appear normal. *Microscopical.*—Floor of 3d ventricle open (cf. Fig. 19); no evidence of pars intermedia or anterior-lobe cells. Thyroid normal.
Observation 22.—Nov. 27, 1908. Gland removed in fragments; constant venous oozing at base; no injury to temporal lobe.	November 28.	32.0	60	Anuria.	....	Recovered from anæsthetic with usual promptness; soon became comatose; infrequent, deep respirations; slow, irregular pulse and subnormal temperature; death at 8 p. m.	18 hours.	Brain under considerable tension; cerebro-spinal fluid bloody; large clot in interpeduncular region, extending backward to foramen magnum. *Microscopical.*—No evidence of hypophyseal cells (serial sections).
Observation 28.—Dec. 4, 1908. Dry, clean operation; gland removed "in toto"; floor of 3d ventricle torn away, followed by cerebro-spinal fluid.	Dec. 5 (9 a. m.) (6 p. m.) December 6.	38.7 35.2 26.0	168 152 48	230 Anuria.	....	Promptly recovered from anæsthetic; 12 hours later was semicomatose; temperature fell 3.5° C. during the day; comatose on 2d day; rectal temperature 12.5° C. below normal; reflexes retained.	48 hours.	No blood-clot at base. Lungs normal. Cloudy swelling of kidneys. *Microscopical.*—A few active-looking pars intermedia cells remain; the cells are large and swollen; many acini filled with colloid. No anterior-lobe cells seen.
Observation 44.—Jan. 19, 1909. Old dog; dura adherent and friable; hæmorrhage; gland removed in fragments; no injury to temporal lobe.	January 20. January 21. January 22.	38.4 36.0 32.0	142 90 80	140 80 60	....	Lethargic; arching of back; subnormal temperature gradually became comatose; no convulsions.	3 days.	Subcutaneous infection of wound. Brain and dura appear normal; large blood-clot at base; no evidence of remaining hypophysis. Lungs and abdominal organs normal. *Microscopical.*—Organizing blood-clot at base; no pars intermedia or anterior-lobe cells found (serial sections).
Observation 51.—Feb. 24, 1909. Old dog; dura adherent and friable; small vessel at base torn while elevating temporal lobe; gland removed in fragments.	January 25.	32.0	92, irregular.	60	....	Animal never entirely recovered from anæsthetic; arching of back; comatose 24 hours after the operation; subnormal temperature; weak, irregular pulse; reflexes retained; death during night.	36 hours.	Brain and meninges appear normal; small blood-clot around stump of infundibulum. *Microscopical.*—A few pars intermedia cells, infiltrated with blood. No anterior cells seen (serial sections).
Observation 52.—Feb. 25, 1909. Dry, clean operation; entire gland removed in one piece; no injury to temporal lobe.	Jan. 26 (9 a. m.) (6 p. m.)	38.6 36.9	208 Not palpable; heart-rate 45 to minute; feeble and irregular.	Anuria.	....	Onset of typical symptoms on day after operation with coma and death during the night.	36 hours.	Brain and meninges normal; base clean; lungs and abdominal organs appear normal. *Microscopical.*—The anterior and posterior lobes have been completely removed; a thin layer of pars intermedia cells remain at base, not active-looking (serial sections). Fig. 20. Thyroid cells columnar; small amount of colloid in acini; a few large swollen cells lying free in acini.

TABLE II.—ADULT TOTAL HYPOPHYSECTOMIES.—Continued.

Case number and operation.	Date.	Temperature.	Pulse.	Urine.		Clinical symptoms.	Duration of life.	Post-mortem conditions.
Observation 53.—March 1, 1909. Old dog; dura adherent and friable; gland removed in fragments; hæmorrhage; injury to 3d nerve.	March 2 (9 a. m.) (2 p. m.)	37.5° C. 30.0	200 Not palpable.	120 cc.	....	Had entirely recovered from the anæsthetic within 2 hours, walked around the room; drank milk and water; gradually became lethargic; was comatose 18 hours after operation.	24 hours.	Brain and meninges appear normal; large blood-clot at base. Lungs normal; cloudy swelling of kidneys. *Microscopical.*—A few pars intermedia cells, surrounded with blood-clot. No anterior-lobe cells seen (serial sections).
Observation 57.—March 10, 1909. Dry, clean operation; good view of gland which was removed in one piece.	March 11. March 12. March 13. March 14.	37.5 37.4 37.7 30.2	100 160 150 Not palpable.	320 50 70 Anuria.	Reduces Fehling's.	Promptly recovered from anæsthetic; took food and water for the first 2 days; arching of back; sugar in urine; became comatose on afternoon of 3d day; general muscular tremors; reflexes retained.	4 days.	Brain and meninges normal; a small blood-clot at base; no evident fragments of the gland remain. Other organs appear normal. *Microscopical.*—No anterior lobe cells seen in examination of serial sections of base; a few pars intermedia cells remain. No striking change in other organs.
Observation 63.—March 18, 1909. Male; dry, clean operation; good view of gland, which was removed "in toto"; Fig. 18.	March 19. March 20. March 21. March 22.	37.6 36.2 36.5 24.0	90 120 60 Not palpable.	160 120 40 Anuria.	....	For 2 days following operation animal was lethargic; arching of back; subnormal temperature; gradually became comatose; rectal temperature registered 14.8° C. below normal; reflexes retained.	4 days.	No blood-clot at base; no evident remains of the gland. Lungs normal; thyroid much larger than normal; other organs appear normal. *Microscopical.*—A few pors intermedia cells remain at base; not active-looking; no anterior-lobe cells seen (serial sections). (Fig. 19.) Liver-cells vacuolated and shrunken around central vein, stain poorly. Thyroid-cells columnar; thrown up in folds; small amount of colloid in acini.
Observation 67.—March 31, 1909. Dry, clean operation; the entire gland was removed in one piece.	April 1. April 2.	38.0 30.2	160 120	70 Anuria.	Reduces Fehling's.	Recovered from anæsthetic with usual promptness; lethargy; arching of back; general muscular tremors; subnormal temperature; coma and death.	48 hours.	Brain and meninges normal. Thyroid slightly larger than usual; parathyroid large and prominent. Lungs normal. Liver, kidneys and pancreas appear normal. *Microscopical.*—The anterior and posterior lobes have been completely removed. A few pars intermedia cells remain at base; not active-looking. Thyroid-cells columnar; many newly formed acini. Liver and pancreas and adrenal appear normal.
Observation 76.—May 5, 1909. Dry, clean operation; entire gland removed in one piece.	May 6 (9 a. m.) (4 p. m.)	36.2 22.0	60 Not palpable.	Anuria.	....	Recovered from anæsthetic; soon became very dull; refused food; temperature subnormal; respirations slow and deep (7 to minute); gradually became comatose.	48 hours.	Wound clean; no evidence of any remaining hypophyseal tissue. Other organs appear normal. *Microscopical.*—A few pars intermedia cells at base; infiltrated with blood; not active-looking; no anterior-lobe cells seen (serial sections). Thyroid, normal; liver, diffuse vacuolation of the cells; nuclei stain well.

TABLE III.—PUPPY TOTAL HYPOPHYSECTOMIES.

Case number and operation.	Date.	Temperature.	Pulse.	Urine.	Weight.	Clinical symptoms.	Duration of life.	Post-mortem conditions.
Observation 58.—March 10, 1909. Dry, clean operation; the entire gland removed in one piece.	March 11. March 14. March 16. March 20. March 25. March 28. March 29. March 30.	38.8° C. 38.8 38.5 38.8 39.2 38.4 38.6 30.2	240 180 130 160 196 140 120 96, weak and irregular.	320 cc. 500 900 1000 500 320 380 40	8¼ lbs. 10 lbs. 10½ lbs. 10½ lbs.	On day following operation animal bright and playful as before; with the exception of a transient polyuria, the puppy remained apparently normal for 19 days; gained 2¼ lbs. in weight; sudden onset of symptoms of cachexia hypophyseopriva; lethargy; subnormal temperature; arching of back; gradually became comatose.	20 days.	Base of brain clean; no evident remains of the hypophysis. Liver, large and friable, dark red in color with numerous opaque areas of necrosis. Other organs seem normal. *Microscopical.*—A few pars intermedia cells remain; no anterior lobe (serial sections). Thyroid-cells cuboidal in shape; greatly swollen; small amount of colloid in acini. Liver-necrosis, usually limited to the center of the lobule. Cloudy swelling of kidneys.

TABLE III.—PUPPY TOTAL HYPOPHYSECTOMIES.—Continued.

Case number and operation.	Date.	Temperature.	Pulse.	Urine.	Weight.	Clinical symptoms.	Duration of life.	Post-mortem conditions.
Observation 59.—March 12, 1909. Dry, clean operation; no bleeding; gland removed "in toto."	March 13. March 14. March 15.	37.7° C. 35.5 29.0	160 136 Not palpable; heart-rate 60 to minute.	300 cc. 160 Anuria.	6½ lbs.	Animal promptly recovered from anæsthetic, and for 24 hours was bright and playful; appetite good; on the morning of the 2d day began to grow lethargic; subnormal temperature; arching of back; refused food; comatose on 3d day; rectal temperature 29° C. (temperature of the room 24° C.); blood pressure low.	3 days.	Complete removal of hypophysis; base clean; no blood-clot; no injury to temporal lobe. Thyroid, lungs, liver, kidney, adrenal, and pancreas all appear normal. *Microscopical.*—No anterior-lobe cells (serial sections); thyroid normal; other organs appear normal.
Observation 60.—March 12, 1909. Entire gland removed in one piece; no operative complications.	March 13. March 14. March 15. March 17. March 19. March 21. March 23. March 25. March 28. March 29.	38.8 38.8 38.4 37.2 36.8 36.2 34.0 33.0 26.0 22.0	162 140 140 80 76 80 80 82 Not palpable. Not palpable.	990 620 340 180 220 85 60 90 Anuria.	12½ lbs. 10¼ lbs.	Transient polyuria; otherwise normal for 3 days following operation; began to grow stupid on 4th day; gradual fall of temperature; arching of back; poor appetite; general muscular tremors; became comatose on 14th day; death on 15th day; temperature 22° C.; no convulsions; cf. Figs. 12 and 13.	15 days.	No evident remains of hypophysis; no blood-clot at base; no injury to temporal lobe. Thyroid appears normal; also lungs, liver, pancreas, adrenal and kidneys. *Microscopical.*—No anterior-lobe cells (serial sections, Fig. 21); a few pars intermedia cells; not active-looking. Other organs normal.
Observation 62.—March 18, 1909. Entire gland removed in one piece; no operative complications.	March 19. March 20. March 21. March 22. March 23.	38.6 38.4 38.2 28.0 20.0	182 165 142 Not palpable. Not palpable.	1500 800 500 60 Anuria.	10½ lbs.	Animal bright and playful for 3 days following the operation; sudden onset of symptoms of cachexia hypophyseopriva.	5 days.	Base clean; no remains of hypophysis to be seen. Lungs normal. Thyroid normal; liver, pancreas, adrenals and kidneys appear normal. *Microscopical.*—No anterior-lobe cells (serial sections); a few pars intermedia cells; other organs appear normal.
Observation 64.—March 22, 1909. Entire gland removed in one piece; no operative complications.	March 23. March 25. March 27. March 28. March 30. April 1. April 3. April 5.	38.6 38.5 38.2 37.2 37.7 38.0 37.8 30.0	152 160 180 108 80 100 60 60	1100 520 380 100 240 260 200 40	9½ lbs. 9¼ lbs.	Bright and playful (Fig. 14) until 24 hours before death; transient polyuria; slightly subnormal temperature for 10 days; sudden onset with coma; fall in temperature; irregular, feeble pulse.	14 days.	Base clean; no evident remains of hypophysis. Lungs, thyroid, liver, adrenals, pancreas and kidneys appear normal. *Microscopical.*—No anterior-lobe cells (serial sections). A few pars intermedia cells. Thyroid normal; also the other organs.
Observation 65.—March 27, 1909. Entire gland removed in one piece; no operative complications.	March 28. March 29. March 30. April 1. April 3. April 4. April 5.	38.6 38.0 40.0 38.9 38.6 38.4 29.0	160 142 156 120 96 80 Not palpable.	200 900 640 280 145 200	9 lbs. 9½ lbs.	Bright and playful until 24 hours before death; transient polyuria; sudden onset of symptoms of cachexia hypophyseopriva on 8th day.	9 days.	Base clean; no evident remains of hypophysis. Thyroid, lungs, thymus, liver, kidneys, pancreas and adrenals all appear normal. *Microscopical.*—No anterior-lobe cells (serial sections). The usual amount of pars intermedia remains; not active-looking. Diffuse vacuolation of the liver-cells.
Observation 70.—April 7, 1909. Entire gland removed in one piece; no operative complications.	April 8. April 9. April 12. April 15. April 18. April 20. April 22. April 23.	38.8 38.6 38.7 38.0 38.2 38.8 38.6 26.0	154 160 147 100 92 120 86 36	600 740 500 200 230 160 140	8 lbs. 7¼ lbs. 7½ lbs.	Bright and playful until 24 hours before death; transient polyuria; sudden onset of symptoms of cachexia hypophyseopriva; gradually became comatose; arching of back; slow, irregular pulse; subnormal temperature; irregular jerking contractions of the depressors of the jaw, and extensors of the fore-legs.	16 days.	Base clean; no blood-clot; no remains of hypophysis. Thyroid looks normal. Thymus and anterior mediastinum œdematous; fatty degeneration of the liver; adrenals and pancreas appear normal; cloudy swelling of kidneys. *Microscopical.*—No anterior-lobe cells (serial sections). A few pars intermedia cells remain at base; many acini distended with colloid-like material; cells swollen. Thymus œdematous and congested with blood; liver fatty; other organs appear normal.
Observation 89.—May 28, 1909. Entire gland removed in one piece; no operative complications.	May 29. May 30. May 31. June 1. June 2. June 3. June 4 (8 a. m.) (4 p. m.)	38.6 38.6 38.5 38.5 38.8 38.2 36.0 33.2	180 136 100 100 120 80 60 Not palpable. (Fig. 16).	500 280 160 120 130 90 80 Anuria.	12 lbs. 11¼ lbs.	Bright and playful (cf. Fig. 15), until onset of symptoms of cachexia hypophyseopriva on 6th day.	7 days.	Base clean; no evident remains of hypophysis. Thyroid, lungs, thymus, adrenals, pancreas and kidneys appear normal; surface of liver contains a few small opaque areas of necrosis. *Microscopical.*—No anterior-lobe cells (serial sections); a few active-looking pars intermedia cells; colloid bodies seem to be passing into 3d ventricle. Thyroid normal; necrosis around central vein in liver; other organs appear normal.

TABLE IV.—REMOVALS OF POSTERIOR LOBE ALONE.

Case number and operation.	Date.	Temperature.	Pulse.	Urine.	Weight.	Clinical symptoms.	Duration of life.	Post-mortem conditions.
Observation 25.—Dec. 4, 1908. Adult bull terrier; male; (Fig. 25); dry, clean operation; removal of posterior lobe and the greater portion of the pars intermedia; no operative complications.	December 5. December 15. December 30. January 30. February 20. March 30. April 30. May 30.	38.6° C. 38.6 38.8 38.6 38.2 38.6 38.4 38.4	150 144 140 120 90 80 60 72	200 cc. 280 350 320 430 360 380 280	18½ lbs. 20 lbs. 20 lbs. 20 lbs. 18¾ lbs. 19½ lbs.	Promptly recovered from operation; remained normal; appetite good; had 2 attacks with general convulsions, salivation and unconsciousness; so erotic that could not be kept in the yard with other animals; sacrificed for the purpose of histological study.	Sacrificed 6 months after operation.	Anterior lobe looks normal; posterior lobe absent. Thyroid, large and firm; other organs appear normal. *Microscopical.*—Posterior lobe removed; many large "colloid bodies" in stalk and in the brain substance around 3d ventricle; anterior lobe appears normal in arrangement and staining; contains a large cyst filled with a faintly bluish staining colloid. Thyroid cells flat; acini distended with colloid; other organs normal. Testicle, active spermatogenesis.
Observation 85.—May 19, 1909. Puppy; Fig. 23; uncomplicated posterior lobe removal.	May 20. May 21. May 22. May 25. May 30. June 5. June 10. June 11.	38.8 38.8 38.2 38.5 38.8 38.6 38.8 36.2	140 160 144 140 152 136 115 120	800 800 420 300 315 260 280 320	10 lbs. 11¼ lbs.	Promptly recovered from operation; transient polyuria; otherwise perfectly normal in every particular for 22 days; bright and playful. On the morning of 23d day animal looked sick; refused food; gradually became comatose; death at 4 p. m.; no convulsions.	23 days.	Well nourished; brain and meninges appear normal; anterior lobe looks normal; posterior lobe removed. Thyroids larger than normal; lungs, adrenals, testicles and kidneys appear normal. *Microscopical.*—Anterior lobe normal in appearance. Liver shows extreme degeneration. Other organs normal.
Observation 86.—May 20, 1909. Puppy; Fig. 24; uncomplicated posterior lobe removal.	May 21. May 23. May 25. May 27. May 28. May 29. June 1. June 5. June 15. June 25. June 30.	38.0 38.2 38.6 38.2 37.2 39.4 38.2 38.4 38.6 38.5 38.3	120 136 132 120 60 90 86 82 76 68 92	580 800 480 185 160 180 200 240 280 300 140	10½ lbs. 12 lbs. 13½ lbs.	Transient polyuria; gain in weight; remained bright and playful; no convulsions; sacrificed 50 days after the operation.	Sacrificed 50 days after operation.	Animal well nourished; anterior lobe appears normal; thyroids and other organs appear normal. *Microscopical.*—Anterior lobe partly destroyed by scar-tissue the greater portion, however, is normal in appearance. Liver, diffuse vacuolization of cells but most marked in center of lobules.

TABLE V.—TOTAL REMOVAL OF ANTERIOR LOBE ALONE.

Case number and operation.	Date.	Temperature.	Pulse.	Urine.	Weight.	Clinical symptoms.	Duration of life.	Post-mortem conditions.
Observation 7.—Oct. 8, 1908. Fox terrier; adult; complete removal of anterior lobe; posterior lobe left in place; dry, clean operation; no operative complications.	October 9. October 10. October 11.	39.2° C. 37.2 32.0	140 116 60, irregular.	420 cc. 80 60	....	Promptly recovered from the anæsthetic; was bright and lively on the day following the operation; symptoms of cachexia hypophyseopriva appeared 48 hours after the operation; animal gradually became comatose; temperature subnormal; pulse slow and irregular; death on third day.	68 hours.	Wound healing per primam. Posterior lobe found in sella turcica; blood-supply intact; surrounded with blood-clot. Other organs appear normal. *Microscopical.*—No anterior-lobe cells found in serial sections of the base; posterior lobe and pars intermedia stain normally. The interstices of the posterior lobe are filled with numerous small "colloid bodies" (Fig. 30), converging at the stalk, and passing upward into third ventricle. Other organs normal.
Observation 9.—Oct. 13, 1908. Bull terrier; adult; total removal of anterior lobe; posterior lobe left in place; dry, clean operation; no operative complications.	October 14. October 15.	39.2 34.0	165 52	140 45	....	Never entirely recovered consciousness; arching of back; subnormal temperature; feeble, irregular pulse.	48 hours.	Wound healing per primam. Posterior lobe found in sella turcica; blood-supply intact; surrounded with blood-clot. Other organs appear normal. *Microscopical.*—Floor of 3d ventricle torn out; no anterior-lobe cells found in serial sections. Posterior lobe lost in sectioning. Other organs normal.
Observation 23.—Dec. 1, 1908. Fox terrier; adult; total removal of anterior lobe; posterior lobe left in place; dry, clean operation; no operative complications.	December 2. December 3.	38.4 29.0	200, irregular. Not palpable.	85 Anuria.	....	The symptoms of cachexia hypophyseopriva were well marked on the day following the operation; animal gradually became comatose.	48 hours.	Wound healing per primam. Blood-clot at base; posterior lobe found in place, appears normal. Other organs appear normal. *Microscopical.*—Specimen removed at operation shows entire anterior lobe and floor of 3d ventricle. Base, no anterior-lobe cells seen. Posterior lobe stains normally; contains many "colloid bodies."

TABLE VI.—STALK SEPARATIONS.

Case number and operation.	Date.	Temperature.	Pulse.	Urine.	Weight.	Clinical symptoms.	Duration of life.	Post-mortem conditions.
Observation 20.—Nov. 25, 1908. Puppy; dry, clean operation; gland separated from base; no operative complications.	November 26.	38.2° C.	192	2000 cc.	....	With the exception of a marked polyuria the animal was apparently normal in every particular for a week following the operation. Sudden onset of usual symptoms of cachexia hypophyseopriva; death at 10 a. m. on December 5.	10 days.	No evidence of infection. Hypophysis adherent to base in normal situation—brilliant red color—no gross changes in other organs. *Microscopical*—Both lobes entirely degenerated and largely replaced by fibroblasts, etc. Patches of normal pars intermedia still apparent. One microscopic clump of stainable anterior-lobe cells at anterior angle. Thyroid and parathyroid show slight hyperplasia; other organs normal.
	November 27.	38.6	160	2260				
	November 30.	38.6	142	1600				
	December 1.	40.0	156	1200				
	December 2.	38.0	92	800				
	December 3.	28.6	51	60				
	December 4.	22.0	Not palpable.	Anuria.				
Observation 33.—Dec. 18, 1908. Fox terrier; adult; same operation.	December 19.	37.2	156	880	14 lbs.	For 10 days following the operation animal was lethargic; temperature slightly subnormal; arching of back; appetite poor, and was rapidly becoming cachectic; was given daily subcutaneous injections—10 cc. of a 1 per cent aqueous extract of anterior lobe of ox—for one month; marked improvement; gained in weight; temperature remained normal and appetite good; was sacrificed on May 10 for the purpose of making histological study of the tissues.	Sacrificed 5 months after the operation.	The hypophysis has become reattached to the base; appears flattened and shrunken. Testicles appear much smaller than normal; other organs seem normal. *Microscopical.*—The hypophysis is surrounded by scar-tissue, and is firmly adherent to the floor of the third ventricle; a thin layer of scar-tissue marks the line of recent division of the stalk (cf. Fig. 28). Anterior lobe contains a large colloid cyst; cells small and brightly stained with eosin. Posterior lobe invaded by down-growths of pars intermedia; many acini filled with colloid. Testicles, many of tubules lined with a single layer of cells; there is a marked increase in the "zwischen-zellen." Other organs normal.
	December 20.	38.0	132	935				
	December 22.	37.8	116	950				
	December 24.	38.2	94	620				
	January 1.	37.4	82	465	12 lbs.			
	January 1 to February 5.—Daily injections (subcutaneous) of a 1 per cent anterior lobe extract; daily amount of urine varied from 240 to 600 cc.; no sugar.							
	February 25.	38.5	136	....	14 lbs.			
	March 29.	38.8	116	380	16 lbs.			
	April 25.	38.5	100	320	17½ lbs.			
	May 10.	38.8	136	260	18 lbs.			
Observation 35.—Dec. 18, 1908. Fox terrier; adult; same operation.	December 19.	38.6	212	1400	....	Transient polyuria; gradual onset of symptoms of cachexia hypophyseopriva, becoming comatose on the 23d day; anuria; diarrhœa; weak, irregular pulse; subnormal temperature (21° C.).	24 days.	The gland has become reattached to the base; surrounded by scar-tissue. Lungs and other organs appear normal. *Microscopical.*—A thin line of scar-tissue marks the site of the recent division of the stalk. Posterior lobe appears normal; a few anterior-lobe cells stain brightly with eosin; pars intermedia cells appear normal. Testicles not examined; other organs normal.
	December 21.	38.5	132	900				
	December 26.	38.2	140	640				
	December 29.	38.8	135	400				
	January 2.	37.2	96	140				
	January 5.	36.8	80	80				
	January 8.	36.4	72	45				
	January 10.	35.0	52	Anuria.				
	January 11.	21.0	Not palpable.	Anuria.				
Observation 83.—May 13, 1909. Bull terrier; adult; same operation.	May 14.	38.4	136	760	....	Transient polyuria; had purulent discharge from both nostrils; sacrificed on June 10; (Fig. 26).	Sacrificed 28 days after the operation.	Wounds healed per primam. Frontal sinus full of pus; areas of bronchial pneumonia in both lungs. Thyroids large and firm. Testicles appear normal. Hypophysis reattached to base; surrounded by scar-tissue. *Microscopical.*—Serial sections of the base of the brain and hypophysis show the separation to have been complete; has become reattached by scar-tissue. Posterior lobe contains many acini of pars intermedia cells filled with colloid; anterior lobe appears normal. Thyroid, large acini filled with colloid, cells flat. Testicles and other organs appear normal.
	May 19.	38.9	84	430				
	May 21.	38.5	100	500				
	May 26.	38.4	72	400				
	June 1.	38.4	64	200				
	June 5.	38.6	72	320				
	June 8.	37.2	52	280				
	June 10.	36.0	60	180				

TABLE VI.—STALK SEPARATIONS.—Continued.

Case number and operation.	Date.	Temperature.	Pulse.	Urine.	Weight.	Clinical symptoms.	Duration of life.	Post-mortem conditions.
Observation 90.—May 29, 1909. Puppy; same operation.	May 30. May 31. June 2. June 4. June 7. June 9.	38.8° C. 38.6 39.2 38.8 38.6 38.8	180 160 80 100 92 86	260 cc. 200 240 250 180 165	....	Promptly recovered from operation, and remained bright and playful; temperature and pulse normal; urine approximately normal; was sacrificed in order to make an histological study of the tissues.	Sacrificed on 12th day after the operation.	Wounds healed per primam. Hypophysis firmly adherent to base, but to the left of its normal situation; surrounded by organizing blood-clot. Thyroids, lungs, liver, adrenal, pancreas, kidneys and ovaries appear normal. *Microscopical.*—Portion of anterior lobe replaced by fibroblasts; the cells of the remaining fragment are large and faintly staining, very few eosinophiles. Posterior lobe very cellular, contains excess of thin colloid and hyaline bodies (cf. Fig. 30). Other organs appear normal.

TABLE VII.—PARTIAL REMOVAL OF PARS ANTERIOR LEAVING POSTERIOR LOBE.

Case number and operation.	Date.	Temperature.	Pulse.	Urine.	Weight.	Clinical symptoms.	Duration of life.	Post-mortem conditions.
Observation 26.—Dec. 4, 1908. Adult cur; partial hypophysectomy; poor exposure; bleeding; about ⅔ of anterior lobe removed; posterior lobe left in place; injury to temporal lobe.	December 5. December 6. December 7. December 8. December 9. December 10.	39.0° C. 38.6 38.8 38.2 36.0 27.0	192 88 112 160 90 Not palpable.	1200 cc. 860 400 150 25 Anuria.	....	Rotary progression; transient polyuria; onset of symptoms of cachexia hypophyseopriva on 5th day; transfusion of blood on 6th day; no improvement; death at 6 p. m.	6 days.	Small blood-clot at base surrounding the posterior lobe and a fragment of anterior lobe. Other organs appear normal. *Microscopical.*—Posterior lobe in place with stalk and blood-supply intact; surrounded by active-looking pars intermedia cells; large number of "colloid bodies" in body of posterior lobe and in the brain substance surrounding the 3d ventricle. A few normal-looking anterior-lobe cells seen (serial sections).
Observation 27.—Dec. 4, 1908. Adult hound; male; partial hypophysectomy; the greater part of the anterior lobe was removed; no operative complications.	December 5. December 10. December 30. January 17. February 25. March 29. April 14. May 5.	38.2 38.3 37.6 38.0 38.5 38.0 38.2 38.4	152 132 140 100 100 60 72 80	2000 1450 1200 750 645 680 450 520	18 lbs. 19 lbs. 21 lbs. 22½ lbs. 24 lbs. 25 lbs. 24 lbs.	Transient polyuria; gain in weight (18 to 24 lbs.); loss of hair; impotence; appetite remained good; entire right thyroid removed on December 15; left thyroid removed on April 30; dull and stupid for several days; refused food; death on May 5; no definite attacks of tetany.	5 months.	Well nourished; hair thin; skin thick and œdematous; brain and meninges appear normal; no evident remains of anterior lobe; posterior lobe in place. No thyroid or parathyroid tissue could be found. Ovaries small, buried in fat. *Microscopical.*—A few active-looking anterior-lobe cells (serial sections); posterior lobe contains many "colloid bodies"; proliferation of pars intermedia. Ovaries small. Contain very few developing follicles. Cloudy swelling of kidneys; other organs normal.
Observation 29.—Dec. 11, 1908. Fox terrier; adult; partial hypophysectomy; an apparently complete removal of anterior lobe; posterior lobe left in place; no operative complications; pneumonia.	December 12. December 15. December 25. January 1. January 15.	38.2 38.2 38.0 38.8 39.8	180 124 120 140 200	650 490 300 240 120	20 lbs. 20½ lbs.	Transient polyuria; no striking gain in weight; apparently normal till January 10; developed a purulent discharge from nose, cough, rapid respiration, etc.; death on January 18.	Death from pneumonia on 38th day.	Wound healed per primam. Lungs consolidated; brain and meninges appear normal; no evidence of anterior lobe; posterior lobe in place. *Microscopical.*—A few active anterior-lobe cells (serial sections). Posterior lobe attached to base by stalk; contains many "colloid bodies." Lungs consolidated; other organs not examined.
Observation 30.—Dec. 11, 1908. Fox terrier; adult; partial hypophysectomy; an apparently complete removal of anterior lobe; posterior lobe left in place; no operative complications.	December 12. December 15. December 30. January 5. January 20. January 24. January 25.	38.6 38.8 38.4 38.0 38.0 32.0 26.0	118 128 72 84 60 42 Not palpable.	800 130 120 160 180 40 Anuria.	14 lbs. 14 lbs.	Promptly recovered from operation; transient polyuria; no gain in weight; sudden onset of symptoms of cachexia hypophyseopriva; temperature fell to 26° C.; arching of back; coma; death at 10 a. m.	45 days.	Brain and meninges appear normal; posterior lobe in place; no evidence of anterior lobe. Other organs appear normal. *Microscopical.*—By a careful search through serial sections of the base a few anterior-lobe cells are found imbedded in scar-tissue. Posterior lobe being invaded by fibroblasts. The specimen removed at operation shows what is apparently the entire anterior lobe. Other organs normal.

TABLE VII.—PARTIAL REMOVAL OF PARS ANTERIOR LEAVING POSTERIOR LOBE.—Continued.

Case number and operation.	Date.	Temperature.	Pulse.	Urine.	Weight.	Clinical symptoms.	Duration of life.	Post-mortem conditions.
Observation 31.—Dec. 11, 1908. Fox terrier; adult; partial hypophysectomy; an apparently complete removal of the anterior lobe; posterior lobe left in place; no operative complications.	December 12. December 15. December 18. December 21. December 30. January 1. January 4. January 5. January 6.	38.6° C. 38.2 38.4 37.8 38.2 38.0 37.4 35.0 27.0	120 126 90 98 80 72 84 58 Not palpable.	800 cc. 620 170 210 100 80 100 40 Anuria.	17½ lbs. 18 lbs.	Transient polyuria; gradual onset of symptoms of cachexia hypophyseopriva; lethargy; subnormal temperature; arching of back; diminished output of urine; coma; death on January 6.	26 days.	Posterior lobe in place; no evidence of anterior lobe; thyroid slightly larger than normal; other organs seem normal. *Microscopical.*—A few anterior-lobe cells surrounded with scar-tissue (serial sections). Finger-like processes of pars intermedia projecting into posterior lobe; many acini filled with colloid; many "colloid bodies" in posterior lobe and stalk. Cells of thyroid are columnar; very little colloid; other organs normal.
Observation 34.—Dec. 18, 1908. Fox terrier; adult; stalk separation and partial hypophysectomy; only a very small portion (about one-third) of anterior lobe was removed; posterior lobe left in place; no operative complications.	December 19. December 30. January 20. February 25. March 4. March 31. April 15. May 10. May 30. June 12. June 14. June 15. June 16. June 17.	38.2 38.0 38.4 37.6 38.2 37.4 38.1 38.6 37.0 38.2 38.6 40.8 40.0 39.8	145 128 100 92 86 76 84 98 120 105 136, injection of anterior lobe. 120 98 120	1200 1520 980 865 675 820 940 1440 1000 1140 880 940 2400 1920	14 lbs. 17½ lbs. 19½ lbs. 19½ lbs. 22 lbs. 22 lbs. 23 lbs. 23¾ lbs. 24 lbs.	Polyuria for six months (675 to 2400 cc. per diem); gain in weight (14 to 24 lbs.); dull; moves slowly and deliberately; not in "heat" for six months; reaction to subcutaneous injection of 3 cc. of a 1 per cent solution of anterior lobe of pig; rise in temperature from 38.6 to 40.8° C.; animal quite sick; polyuria (2400 cc. for 24 hours); animal sacrificed on June 17.	Sacrificed at end of 6 months.	Animal very fat. Brain and meninges look normal; hypophysis slightly smaller than normal; firmly adherent to floor of 3d ventricle. Thyroids are about normal in size; lungs normal; fatty degeneration of heart muscle; liver is greyish-white in color (fatty degeneration); fatty degeneration of kidneys; other organs appear normal. *Microscopical.*—About two-thirds of the anterior lobe remains at base; vessels, prominent, running between strands of eosinophilic cells (smaller than normal); many collections of nuclei, without protoplasm. Posterior lobe invaded by finger-like processes of pars intermedia cells; many of the acini contain colloid-like material. Fatty degeneration of myocardium, liver and kidneys. Pancreas appears normal. Ovary contains many developing ovules, and the remnants of three lutean cysts.

TABLE VIII.—PARTIAL ANTERIOR WITH TOTAL POSTERIOR LOBE REMOVALS.

Case number and operation.	Date.	Temperature.	Pulse.	Urine.	Weight.	Clinical symptoms.	Duration of life.	Post-mortem conditions.
Observation 43.—Jan. 14, 1909. Fox terrier; adult; partial hypophysectomy; a fragment of anterior lobe was unintentionally left at the base.	January 15. January 16.	36.2° C. 25.8	60 Not palpable.	150 cc.	....	Never entirely recovered from anæsthetic; subnormal temperature and slow irregular pulse, which finally became so feeble that it could not be palpated; death at 11 a. m.	1½ days.	Wound clean; large blood-clot at base; a small fragment of anterior lobe remains attached to base. Other organs appear normal. *Microscopical.*—Serial sections of the base show a few anterior-lobe cells infiltrated with blood (not active). Cloudy swelling of kidneys; other organs normal.
Observation 49.—Feb. 23, 1909. Fox terrier; adult; partial hypophysectomy; a fragment of anterior lobe was unintentionally left at the base.	February 24. February 25. February 26. March 1. March 5. March 8. March 11. March 13.	36.6 36.6 37.8 38.6 38.8 38.0 38.6 38.4	140 180 120 92 115 100 120 136	120 60 145 160 200 120 165 190	....	Symptoms of cachexia hypophyseopriva for three days following the operation; gradually recovered and was sacrificed on 21st day following operation.	Sacrificed 21 days after the operation.	Organizing blood-clot at base; no recognizable hypophyseal remains. Thyroid large and soft; other organs appear normal. *Microscopical.*—Serial sections of base show a small island of active-looking anterior-lobe cells surrounded with scar-tissue; the cells are large, finely granular, with vesicular nuclei. Thyroid cells columnar; acini contain but very little colloid. Other organs normal.

TABLE VIII.—PARTIAL ANTERIOR WITH TOTAL POSTERIOR LOBE REMOVALS.—Continued.

Case number and operation.	Date.	Temperature.	Pulse.	Urine.	Weight.	Clinical symptoms.	Duration of life.	Post-mortem conditions.
Observation 54.—March 1, 1909. Spaniel; adult; male; (Fig. 39); partial hypophysectomy; a small fragment of anterior lobe was left; no operative complications.	March 2. March 3. March 5. March 30. April 20. May 20. June 15.	38.5° C. 39.3 38.2 38.6 38.6 38.8 37.6	130 128 110 128 136 140 132	500 cc. 1600 950 1200 860 900 780	16 lbs. 18 lbs. 25¾ lbs. 27 lbs. 27 lbs.	Transient glycosuria; polyuria (500 to 1600 cc.) continued for 3½ months; gain in weight (from 16 to 27 lbs.); for a week following the operation animal was dull, sleeping heavily most of the time; began to improve, and for the remaining three months was very lively and playful; intravenous injection of 3 cc. of 1 per cent aqueous extract of anterior lobe (pig) caused a marked rise in blood pressure and body temperature.	Sacrificed 3½ months after the operation.	Animal very fat. Brain and meninges appear normal; no recognizable remains of the hypophysis. Thyroids appear normal; fatty degeneration of liver; pancreas, adrenals, ovaries and kidneys appear normal. *Microscopical.*—A small area of active-looking anterior-lobe cells surrounded by scar-tissue (serial sections). Thyroid cells flat; acini distended with colloid. Other organs appear normal.
Observation 55.—March 3, 1909. Fox terrier; adult; male; (Figs. 40, 41); partial hypophysectomy; a small fragment of anterior lobe was unintentionally left.	March 4. March 5. March 6. March 30. April 30. May 30. June 15.	38.5 39.0 38.5 38.2 38.4 38.2 38.4	165 120 76 88 88 72 92	1100 870 230 460 580 640 800	17 lbs. 18½ lbs. 21½ lbs. 23 lbs.	Polyuria (340 to 1100 cc.) for 3½ months; atrophy of testicles (cf. Fig. 40); gain in weight (17 to 23 lbs.); intravenous injection of 3 cc. of 1 per cent aqueous extract of anterior lobe (pig) caused a rise in blood pressure, marked increase in respirations, and a subsequent rise in temperature (38.4 to 42.5° C.).	Sacrificed 3½ months after the operation.	No recognizable remains of hypophysis; thyroid, liver, adrenals and kidneys appear normal. Testicles about half the normal size. *Microscopical.*—A few normally-staining anterior-lobe cells surrounded with scar-tissue (serial sections); thyroid cells of normal size; acini distended with colloid. Testicles, absence of spermatogenetic cells.
Observation 61.—March 16, 1909. Puppy; (Fig. 35); partial hypophysectomy; a small fragment of anterior lobe was unintentionally left at the base.	March 17. March 20. March 30. April 10. May 10. May 12. May 15.	38.5 38.6 38.8 38.3 37.3 36.5 35.8	184 142 160 128 112, distemper. 100 86	740 185 100 150 180 60 45	5½ lbs. 6½ lbs. 7½ lbs.	Promptly recovered from operation; transient polyuria; was apparently normal in every particular for six weeks; gained 2 lbs. in weight; was growing rapidly; distemper; sudden appearance of symptoms of cachexia hypophyseopriva on May 10 (Fig. 35); gradually grew worse; subnormal temperature; arching of back; weak, irregular pulse, and coma.	60 days.	Base of brain contains a thin layer of scar-tissue; no recognizable hypophyseal remains; other organs appear normal. *Microscopical.*—Small group anterior-lobe cells in scar-tissue; large and active in appearance. Few active-looking pars intermedia cells. Liver cells around central vein vacuolated and stain poorly; other organs show no marked changes.
Observation 66.—March 28, 1909. Puppy; partial hypophysectomy; a fragment of anterior lobe was unintentionally left at the base.	March 29. March 30. April 5. April 10. April 15. April 25. May 1. May 3. May 4.	38.6 38.9 38.6 38.5 37.5 37.8 37.0 26.0 17.5	185 160 136 148 84 60 90 Not palpable. Not palpable.	1260 980 800 1240 420 200 105 Anuria. Anuria.	10½ lbs. 12¾ lbs.	Promptly recovered from anæsthetic, and with the exception of polyuria was normal in every particular for 2 weeks following the operation; gained 2¼ lbs. in weight; gradually became lethargic; slowly falling temperature; arching of back; slow, irregular pulse; became comatose on May 3; death on May 4 at 11 a. m.	37 days.	Brain and meninges appear normal; no remains of the hypophysis seen on gross inspection. Testicles much smaller than those of a control puppy of the same age. Liver necroses. *Microscopical.*—A few anterior-lobe cells of the large-active type can be seen surrounded with dense scar-tissue (serial sections). (Fig. 36.) Thyroid normal. Liver cells vacuolated around central vein. Other organs normal. Testicles, tubules lined with single layer of cells; no spermatogenetic cells.
Observation 71.—April 12, 1909. Adult black and tan bitch; Fig. 38; partial hypophysectomy; a fragment of anterior lobe was unintentionally left.	April 13. April 15. April 25. May 10. May 30. June 10.	38.0 38.2 38.8 38.6 37.8 38.0	165 142 120 80 72 60	1100 1520 460 200 340 280	....	Animal promptly recovered from the operation, and with the exception of a transient polyuria seemed normal in every way; sacrificed June 10.	Sacrificed 58 days following the operation.	Well nourished; wound healed per primam. Base of brain clean; no evident remains of the hypophysis. Areas of focal necrosis in liver; other organs appear normal. *Microscopical.*—Anterior-lobe fragment found buried in scar-tissue at the base (serial sections); other organs normal.
Observation 80.—May 10, 1909. Adult cur; Fig. 8; partial hypophysectomy; the posterior lobe and about two-thirds of anterior lobe removed; no operative complications.	May 11. May 15. May 30. June 21.	38.6 38.6 38.2 38.6	160 92 82 90	1000 820 400 240	11 lbs. 12 lbs. 12½ lbs.	Promptly recovered from operation; transient polyuria; gain of 1½ lbs. in weight; seemed normal in every particular when sacrificed on June 21.	Sacrificed 42 days following the operation.	Wound healed per primam; about one-third of anterior lobe remains at base; other organs appear normal. *Microscopical.*—Remains of anterior lobe seems normal in every particular; the majority of the cells are small and closely packed with brightly red-staining granules. Other organs normal.

TABLE VIII.—PARTIAL ANTERIOR WITH TOTAL POSTERIOR LOBE REMOVALS.—Continued.

Case number and operation.	Date.	Temperature.	Pulse.	Urine.	Weight.	Clinical symptoms.	Duration of life.	Post-mortem conditions.
Observation 81.—May 12, 1909. Adult black and tan; partial hypophysectomy; a fragment of anterior lobe was unintentionally left; no operative complications. (Fig. 38).	May 13. May 15. May 30. June 14.	38.6° C. 38.6 38.2 38.2	182 86 72 86	300 cc. 260 240 180	14 lbs. 15 lbs. 16 lbs.	No polyuria; no symptoms of cachexia hypophyseopriva; gain of 2 lbs. in weight; a kymographic record of blood pressure and respiration was taken during this operation (cf. Fig. 7); sacrificed on June 14.	Sacrificed 32 days following the operation.	Animal well nourished; no evident remains of the hypophysis; ovaries small, surrounded with fat; other organs appear normal. *Microscopical.*—Dense scar-tissue at base with normally staining anterior-lobe fragments, cells of which appear to be in the active stage of secretion (serial sections). Other organs normal.
Observation 88.—May 27, 1909. Fox terrier; adult; partial hypophysectomy; dura adherent and friable; venous bleeding at base; apparently the entire gland was removed at operation.	May 28. May 29. May 31. June 2. June 4. June 5. June 8. June 10.	37.2 37.6 37.2 37.0 38.4 38.8 38.3 38.6	160 180 90 82 100 88 80 96	580 460 650 580 900 820 500 430	....	Symptoms of cachexia hypophyseopriva appeared immediately after the operation (lethargic subnormal temperature; arching of back; refused food); gradually recovered and from June 4 to 10 was apparently normal.	Sacrificed 12 days following the operation.	Organizing blood-clot at base; no evident remains of the hypophysis. Thyroid large and firm; other organs appear normal. *Microscopical.*—Base, organizing blood-clot with a small area of very much swollen, active-looking anterior-lobe cells; colloid goitre; other organs normal.
Observation 98.—June 11, 1909. Black and tan bitch; partial hypophysectomy with fragment left; weight 13½ lbs.	June 12. June 22. September 25. December 15. March 15.	38.2 38.2 .... Sacrificed.	160 116	1100 500 600 800	13¼ lbs. 12¾ lbs. 18½ lbs. 20½ lbs. 24½ lbs.	Transient polyuria and slight loss in weight immediately following operation; not observed during summer; three months later had thick skin, scant hair, dull and stupid, fat; continued to gain in weight; never in heat; definite temperature reaction following subcutaneous injection anterior lobe extract.	Sacrificed after 9 months.	No evident remains of gland; abundant subcutaneous fat; skin thick; thyroid large and colloidal; ovaries small; uterus represented by a shred of tissue. Other organs apparently normal. *Microscopical.*—Minute fragment of anterior lobe in scar-tissue and a few pars intermedia cells (cf. Fig. 42). Pancreas, islands of Langerhans prominent, cells swollen. Thyroid, colloidal. Ovaries, under-developed. Adrenal, medullary cells large and active in appearance.
Observation 100.—June 15, 1909. Fox terrier; adult; partial hypophysectomy; a fragment of anterior lobe was unintentionally left at the base; no operative complications.	June 16. June 18. June 21.	38.4 38.2 38.5	142 78 109	1000 800 640	....	Lethargic; appetite poor; general muscular tremors (rate about 200 to minute); polyuria (640 to 1000 cc.); no sugar in urine; sacrificed June 21.	Sacrificed 6 days following the operation.	Wound healed per primam. A small fragment of anterior lobe remains at base, surrounded with blood-clot; other organs appear normal. *Microscopical.*—The minute remaining fragment of anterior lobe contains normally-staining cells; other organs normal.

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CONTENTS.

SIR CHARLES BELL: THE MAN AND HIS WORK.*

By Eugene R. Corson, M. D., Savannah, Ga.

Veniet tempus quo ista quæ nunc latent, in lucem dies extrahet, et longioris ævi diligentia. Veniet tempus quo posteri nostri tam aperta nos nescisse mirabuntur.

A careful study of an ordinary human life is not without interest and brings with it at times a deep lesson. And when a life happens to be that of genius, of one who, in his time and generation, stood out in bold relief, and who left us the products of his genius to be admired and wondered at, its study becomes indeed of absorbing interest.

There has been a tendency for some years to dwell upon the dark side of genius (if there is such a side), to study the eccentricities and morbidities which have attended certain forms of genius. Minute studies have been made of mental and physical stigmata in the hope of following the radiance to its source, but I have failed to see that any light has come from this work. It has been a quest of epiphenomena alone. There is a notable example of this in a large work by Max Nordau, entitled "Degeneration," in which this writer has brought together with an interminable analysis all the cases he could find of any perversions, eccentricities, or insanities connected with genius in any form. The genius itself was not only placed in the background, while insanity or degeneration stood boldly in the front, but the writer has failed to give us the slightest guiding thread that we could follow up.

It is well for the world that genius compels its full recognition and acceptance, though these be at times delayed, and that, whatever morbid or eccentric accompaniments there may be, they pertain to the outer man, while the real radiance of genius itself shines steadily on with undiminished splendor.

But a greater than Max Nordau, namely, F. W. H. Myers, who was himself a genius, has given us a truer and loftier conception of the divine gift. He who would learn more of the absolute character of genius should make a careful study of that great chapter on the subject in his "Human Personality." He would get a point of view which would illumine the dark passages through which genius may at times have had to pass; he would better understand genius as in a way apart from the mere discursive intellect, an "uprush" from

* Paper read before the Johns Hopkins Hospital Historical Society, December 13, 1909.

the diviner self, and *sufficient unto itself;* and he would better understand what seemed incomprehensible before—the functioning and life of this deeper and greater self. What to Nordau were the intimate and inseparable associates of genius will now be seen to be things apart from it, and standing in the way of the roseate glow of its morning and the clear white light of its high noon.

The subject of our present sketch shows us a harmony, an equipoise of the moral, emotional, and intellectual man quite as rare as the quality of his genius. I have looked in vain into the sources at my disposal for the disturbing factors to the full play of his powers. On the contrary, I found a deep religious nature, great optimism with great confidence in self, an artistic temperament with a critical and philosophical faculty, a keen appreciation of literature and poetry, a capacity for great affection and love of family, with ambition and high ideals, and great energy and industry; and, as a basis for all these qualities, an absorbing passion for the study of structure, of anatomy, human and comparative, with the genius of the naturalist for observation—all marshaled around his one great, absorbing study, the work of his life, the making of a great anatomist and surgeon.

His genius ranks him with the great observers of nature, wholesome, finely poised, of simple living and high thinking. The faithful study of nature seems to lead to a certain calm happiness and contentment. The eagerness and joy of observation, the joy of discovering the causes of things seems to transcend all else, be the quest in the woods and fields, or within the closed walls of a laboratory or dissecting room. Of this the life of Charles Bell gives us abundant evidence.

Charles Bell's grandfather was a Mr. John Bell, minister of Gladsmuir, who was born on February 2, 1676. He was noted for his industry, determination, and impressive eloquence. He was called upon to preach the sermon on the death of William III before the General Assembly of the Church of Scotland. That he gained a reputation for a vigorous intellect before he was thirty shows him to have been a man of parts. He died at the early age of thirty-two, leaving several children, of whom William Bell alone comes into prominence as the father of Charles, and as a member of the Catholic and Apostolic Church of Scotland. To have left the Presbyterian Church, of which his father and family were members, and to have become a minister of the Episcopal Church of Scotland, at a time when that church was under many restrictions and persecutions, shows his independence and fearlessness. His first wife, surviving all her children, died in 1750. In 1757 he married Margaret Morice, the elder daughter of an Episcopal clergyman. Early left an orphan, she was educated by her grandfather, Bishop White, afterwards Primus of Scotland. She was distinguished for her piety and many accomplishments, among which was a great talent of drawing which she transmitted to her children. It was in her youngest son, Charles, that this talent of the family culminated.

William Bell died on September 20, 1779, aged 75 years, leaving a wife and six children very slenderly provided for.

In memoranda jotted down by George Bell, the fourth son, and most beloved brother of Charles, and who afterwards rose to distinction as a jurist and professor of law in the University of Edinburgh, we read:

"My mother was a most excellent woman, well educated, and of sweet disposition. Left with a large family of children, she struggled with great virtue and fortitude against distresses which I did not at the time understand, but cannot now call to mind without bitter regrets and sorrow. In myself and my dear brother Charles she had her greatest comfort in her later days. . . . . This is a consolation to me which the wealth of worlds would not induce me to forfeit. Our circumstances were so narrow that my education was much stinted—the rest of the family expenses having gradually increased so that my schooling, which required no more than five shilling a quarter, could not be continued after I was eleven years old."

Charles's description of his mother shows her to have been a remarkable woman, gifted in many ways, of great nobility of character, the worthy mother of distinguished sons. Of her six children three reached distinction: John Bell, the anatomist and surgeon; George Joseph Bell, professor of the law of Scotland in the University of Edinburgh; and most distinguished of all, her youngest son, Charles.

Between George and Charles there existed a brotherly love which is hardly to be paralleled in history. For nearly forty years, at short intervals, they kept up an intimate and affectionate correspondence. Each wrote to the other as his *alter ego,* and from the letters of Charles which have been preserved we have a *journal intime* which gives us a clear and detailed picture of the man and his work. It is from these letters that I have been enabled to learn what manner of man he was. From November, 1804, when he went to London, until August, 1836, when he returned to Edinburgh, we can follow him in his work and in his rise to fame; we may know the motives which prompted him, the emotions which stirred him; we may know how he viewed his fellow man and how he treated him. In my search I found nothing unworthy of a noble character. Linked with a life-long serious work, of great industry and great endeavor, of a sustained interest and an enthusiasm which never flagged, we find an almost boyish cheerfulness and freshness of emotion as bright and cheery as a May morning.[1] And in the last years of his life he went a-fishing, whenever he could get a holiday, with all the ardor

[1] In Pichot's Life of Sir Charles Bell, he gives the impression of a melancholy and even misanthropic nature at times, especially in the last years at Edinburgh, when income did not keep step with honors and position and their responsibilities. He evidently got his impression from stray thoughts in the correspondence. It would be impossible to imagine an intense nature like Sir Charles Bell's without an occasional swing of the pendulum towards depression,—almost a normal reaction or relaxation from the accustomed high tension. Sir Charles Bell's family and friends protested against this view as absolutely false; and Lord Cockburn, a most intimate friend, wrote to Lady Bell: "If I ever knew a generally and practically happy man, it was Sir Charles Bell."

And Lord Jeffrey, a very close friend of Sir Charles, wrote to Lord Cockburn on hearing of his death: "This is a sad blow, the loss of good, kind-hearted, happy Charlie Bell."

of a boy. Verily, we have much to learn from this man quite aside from his new physiology of the nervous system.

Charles Bell was born in November,[2] 1774, and was but five years old when his father died. Years afterwards he wrote:

"I received no education but from my mother, neither reading, writing, cyphering, nor anything else. My education was the example set me by my brothers. There has been, in my day, a good deal said about education, but they appear to me to put out of sight *example*, which is all in all. There was in all the members of the family a reliance on self, a true independence, and by imitation I obtained it. . . . .

"When I look back to those days my affection centers in my mother, and in my dear brother, George. Yet Robert was most kind to me. I was his playfellow and pet.

"My first recollections are as a little boy, by my mother's side. I recollect the dining-room, the view south, the mild affection with which she would stop her wheel, or point the letters (of my lesson) with her stocking-wire.

"I must have been either wise or cunning in those days, for having offended her, I did not attempt reconciliation all at once, but I watched her out, and presented myself to her whilst picking her way in the crowded street, when her open arms and benevolent smile received me. . . . .

"She must have been well educated for her time. I know no more of the motions of the earth, moon, and stars, than her little contrivance then taught me as a boy. I recollect the room and the spot where she formed a ball, and passed a stocking-wire through it to show me the poles and the revolutions of the seasons, and gave me the first idea of a truth which the mere senses could not convey, the motion of all which seemed stationary in the diurnal and annual motions of the earth.

"The education at the high school, which I attended for two years, was to me torture and humiliation. Adams, loved by all good scholars, was to me a stupid tyrant. I can remember brightening on the display of Cæsar's Bridges over the Rhine. Anything demonstrative or mechanical, or tending to Natural Philosophy, I comprehended better than my companions; but the memory of verses or Latin rules, without intellectual comprehension of some principles, I was almost incapable of. . . . .

"Memory should be cultivated. It bestows great advantages. Mine was ever deficient. I could not, and cannot venture on a quotation either in conversation or in public discourse. Quotation directed with good taste, gives interest and elegance; but memory, without the direction of sound judgment, is a poor substitute for reason."

We have evidence that he was a good Latin scholar. His "Anatomy of Expression" has many quotations from classic Latin writers. In one of his letters to his brother, he writes: "I have within the last few days read the whole of the Æneid, and have scored some beautiful passages." And again: "I am reading Horace. The Ars Poetica is more worthy of the annotations of a painter than Du Fresnoy's Art of Painting." He got later French and Italian masters to read and speak with him, and he had a fairly free and easy knowledge of both these languages. His appreciation of poetry and literature in general was keen. He quotes repeatedly from Dante and Spencer, whose Faerie Queene was always a favorite with him. He saw in its beautiful imageries so many subjects for his pencil and brush.

[2] I have not been able to find the day of the month of his birth.

His artistic talent which, as is usually the case, he showed as a child, he made use of in his anatomical and surgical studies to an extent and perfection which give a charm to-day to all his writings. His range was so great, from the detailed drawings of the most delicate and intricate dissections, from drawings of pathological specimens, to face and figure drawings illustrating human emotions and expressions. He worked equally well with the pencil, by etching, in water-color, or in oil, and he modeled in plaster and in wax. That he had good composition may be judged from his landscapes, and such pictures as "The Suter and the Sow" and "The Fisher." Examine any little bit of drawing in his surgery or anatomy and you will find the same care and delicacy of touch that you find in his more pretentious drawings. If he draws for you a probe passing under the fascia it is with a realism and an accuracy almost photographic. I am glad to see that this artistic method is being carried out to even greater perfection in our anatomical and surgical illustrations to-day, and if I mistake not, we owe much of this artistic revival to the publications emanating from the Johns Hopkins University, and from the pencil and brush of Max Brödel.

Of his early training he wrote:

"Allen, the painter, was a man very dear to me in my early boyhood. There was sunshine the afternoon he came to me. He was quite a man to a boy's humour. He was wont at all times to salute me, "Ha! Brother Brush, let's see what you have been doing!" To him I am very principally indebted for my pleasure in drawing. . . . . He gave me his very beautiful studies from the Antique, and from Raphael's cartoons, to copy, and was very good natured in his praise. I meet with these heads sometimes, and hail them as something very old and very melancholy sweet."

He was two years in the high school and two years in the University of Edinburgh before he took up seriously the study of medicine. As he himself admits, he did little or nothing to attract attention while at school. Such a mind as his is apt to be too independent and too much absorbed in its own line of thought to follow the set lessons of the schoolmaster.

That he had early mapped out his work and had started to carry it through we have abundant evidence of, for while a medical student he began his "System of Dissections." This was in the spring of 1797, when he was but twenty-three. My own copy of this work, two volumes bound in one, large folio, is dated 1799 on the title page of the first volume, 1800 on the title page of an appendix to Volume I, and 1803 as the date of the second volume. It is a remarkable work for a mere youth. The beautiful drawings of his dissections,[3] the clear descriptive text, the careful instructions of methods of work, show the maturity of genius. You see already the qualities which characterized his more mature and best work, especially his study of function with structure, structure always suggesting function to his mind. This quality was the keynote of all his discoveries and best work. He could not study anatomy without being a physiologist and a philosopher at the

[3] One of the illustrations is his own etching, and a very creditable piece of work, representing an injected preparation of the breast.

same time.[4] He writes in the preface: "The object of this work is to serve as an assistant to the student in acquiring a knowledge of practical anatomy; in gaining a local memory of the parts; in learning to trace them upon the dead subject, and to be able to represent them to his own mind upon the living body. This being my object, the method to be pursued is obvious: to give a short detail of the anatomy; to show how the parts are to be laid open and how they are to be distinguished in dissection, or avoided in an operation; *to explain the consequence of each part to the great functions of the body;* [5] and to mark the diseases to which it is liable."

He has given us in this quotation the secret of a great anatomist, *i. e.*, "in gaining a local memory of the parts; in learning to trace them upon the dead subject, and to be able to represent them to his own mind upon the living body." No more appropriate words could be cut in stone over the doorway of an anatomical laboratory. You must be a good visualizer to be a good anatomist.

I think it is evident that Joseph Maclise, who published his admirable surgical anatomy in 1851, although a distinctly individual book, fashioned it in a general way after this work. Maclise's book is, to my mind, a more practical work to-day than many later books on the subject. The drawings, however, lack the artistic quality and charm of the older work. The comparison of the two is highly suggestive; there may be talent in the one, there is surely genius in the other.

Bell must have graduated in 1799, for on August 1 of that year he became a fellow of the Royal College of Surgeons of Edinburgh. This fellowship put him on the surgical staff of the Royal Infirmary, and in this position he gave evidence of his ability as a practical dissector and anatomist and surgeon, making his own beautiful drawings in his own inimitable way, and preparing anatomical, physiological and pathological specimens for the museum. He invented a method of making models of morbid parts which may still be seen in the museum of the college.

In 1802 he published a series of engravings of original drawings of the anatomy of the brain and nervous system from dissections made for the course in anatomy of his brother John. In 1804 he wrote Volume III of The Anatomy of the Human Body, by John and Charles Bell. The volume deals with the anatomy of the nervous system and the organs of special sense and of the viscera. Thus early was he preparing the way for his discoveries.

In 1804, by some new arrangement, Bell was excluded from the hospital, others getting the appointments by virtue of their seniority. He offered to pay the hospital £100 a year and to transfer to it the museum he had collected on condition that he be "allowed to stand by the bodies when dissected in the theatre of the infirmary, and to make notes and drawings of the diseased appearances." Strange to say, this proposal was rejected and he went to London in November, 1804, probably in large measure influenced by the advice of his brother George. Before he went to London he had largely written a work on "The Anatomy of Expression in Painting." [6] It was published two years later and at once attracted attention as an original and notable work on the subject.

In succeeding editions he added much to it, especially after his Italian journey in 1840, thirty-four years later, when he introduced many of his admirable notes on Italian Art and the Antique. From his letters it can be seen how carefully he made his illustrations. The subject was admirably adapted to his genius, embracing, as it did, the work of the anatomist, the philosopher, and the painter. His dissections of the facial muscles and nerves at once suggested their functions, and he eagerly sought to combine function with structure, and to work out, along artistic and psychological lines, the whole subject of human expression. His keen observation and subtile intuition carried him beyond the mere facial expression. He saw how large a part respiration took in the expression of the emotions, as well as the attitudes assumed by the entire body. This was evidently the basis of that greater study and discovery of the nerves of respiration which was soon to follow.

In the first essay on the form and proportions of the skull and bones of the face he showed how fallacious was the facial line of Camper and the method of Blumenbach in taking the frontal bone and the superior maxillary as a criterion of the development of the brain case. He offered as a better method the following:

"To find a line which should not vary, but enable us to measure with correctness the angles both of the facial line, and of the line intermediate between the cranium and the face, I poised the skull upon a perpendicular rod, by passing the point through the foramen magnum into the interior of the skull, so that the upper part of the cranium rested on the point. By shifting the skull till the rod was exactly betwixt the condyles of the occipital bone, and in the center of the foramen magnum I procured the line which was wanted."

This was a distinct advance in craniology and in the proper estimate of the development of the head as a whole.

His chapter on the theories of ideal beauty shows a fine artistic feeling and knowledge of the history of art. In the chapters on expression in reference to the body he brought out the intimate connection of the respiration and the attitude

[4] We therefore find him using the comparative method as far as comparative anatomy at that time permitted. The great progress made in anatomical study since Bell's time has been based upon comparative anatomy, embryology, and the use of the microscope. I have looked in vain for any mention of the microscope in any of Bell's works. In his careful dissections of the brain and cord it would have seemed most natural had he pushed on his investigations by the use of all the magnifying power at that time obtainable; yet not once is the microscope mentioned, nor does any drawing show microscopic work. His gross anatomy seemed to him all sufficing.

[5] Italics mine.

[6] The title was changed in succeeding editions to "The Anatomy and Philosophy of Expression as Connected with the Fine Arts." The seventh edition appeared as late as 1893. He made many changes and additions especially after his Italian journey in 1840. Many Latin quotations and several striking illustrations were discarded and the work practically rewritten, so that the edition of 1844 is really a new work and shows how diligently he worked to improve his illustrations and his whole treatment of the subject.

Painted by Anthony Stewart, Edinburgh, 1804

SIR CHARLES BELL, AET. 30

From a posthumous bust by Theed

Charles Bell.

of the body with the facial expression. In the two concluding essays he showed the value of anatomy to the painter, and as necessary to design. The illustrations show some of the finest specimens of his pencil. Even in this day of many pictures you can pick out some worthy of reproduction and enlargement. Note the head of the laughing child which closes the Introduction, the merest sketch, yet full of charm. The book had a ready sale and added much to his reputation. In a letter of August 17, 1806, he wrote:

"My book, the Longmans say, moves off. Lynn says everybody talks highly of it, and it is the very thing. 'They don't understand it,' he adds, 'more than myself, but they admire it.'"

At this time he gave lectures to painters on artistic anatomy, teaching them by dissections and on the living model, and with his own beautiful models in clay and wax. Sydney Smith at this time wrote to Jeffrey:

"I hope to see more of your friend Bell. He is modest, amiable, and full of zeal and enterprise in his profession. I could not have conceived that anything could be so perfect and beautiful as his wax models. I saw one to-day which was quite the Apollo Belvedere of morbid anatomy."

It was soon after he came to London that he instituted his own private courses of lectures on anatomy, and later his surgical lectures and the operations of surgery on the cadaver. Many of his students were private pupils living in his own home with him and directly under his personal care. Teaching was ever a passion with him, and he fully realized the stimulation he got from it and its constant incentive to original research. He often referred to the joy of this work, and pointed with pride to the fact that he had educated in anatomy and surgery over eight hundred students.

In a letter of March 7, 1805, the year after he went to London, he wrote: "Longman made me an offer of £300 for two 8vo volumes introductory to surgery." This is good evidence of his progress and the recognition of his ability. The first edition was published in 1807, and the second in 1814. Though the book was evidently a "pot boiler," as the expression goes, and a task which took him away from more agreeable and profitable work, as he admits in his preface, it is a notable book, gives us a very clear and comprehensive view of surgery at that time, but, more important still, shows us his own qualities as a surgeon. As indicated on the title page, the work was a system of operative surgery *founded on the basis of anatomy,* carrying out what his brother John had already forcibly contended for and developed in his own practice. The idea marked a distinct advance in surgery; it was a change from blind cutting to careful dissection and more deliberate operating; it was an advance, however, which only the discovery of anæsthesia a few years after Bell's death thoroughly established and made possible under all circumstances. In no operation at the time was this position more clearly shown and developed than in that of lithotomy. It is very evident here that Bell's surgical acumen carried him ahead of his time. The gorget was still in use, and the operation, though an improvement over the wild, blind jab of Frère Jacques, was still haphazard. The unsurgical operation of Frère Cosme was still practised at the Westminster Hospital by well-known surgeons. Against the gorget and this latter operation Bell strongly contended, and argued for the operation with the knife, a deliberate incision through perineum and prostate, with a clear idea at every step where you are. The operation is very clearly described and the use of the knife illustrated by his characteristic sketches. He used three instruments, a large staff, a scalpel with a straight back, and the usual lithotomy forceps. He described this operation on a boy. "The boy was only three minutes and a few seconds on the table, and was entirely recovered in three weeks." In his description of the operation for hernia we are conscious of the same admirable judgment and surgical skill.

When M. Roux, the great French surgeon, returned home from a visit to London, he wrote:

"Charles Bell is one of the few Englishmen who operates like a Frenchman, quickly and with *grace*, without affectation." [7]

In a letter to his brother on November 26, 1807, he wrote:

"I have done a more interesting nova anatomia cerebri humani than it is possible to conceive. I lectured on it yesterday. I prosecuted it last night till one o'clock, and I am sure it will be well received."

This is the first written record we have of Bell's discovery. Of the great importance of this discovery he was well aware, for on November 31 he wrote:

"I really think this new Anatomy of the Brain will strike more than the discovery of the Lymphatics being absorbents."

On December 5, he wrote:

"My new Anatomy of the Brain is a thing which occupies my head almost entirely. I hinted it to you formerly that I was *burning*, or on the eve of a grand discovery.

"I consider the organs of the outward senses as forming a distinct class of nerves from the others. I trace them to corresponding parts of the brain, totally distinct from the origins of the others. I take five tubercles within the brain as the internal senses. I trace the nerves of the nose, eye, ear, and tongue to these. Here I see established connections. Then the great mass of the brain receives processes from these central tubercles. Again the greater mass of the cerebrum sends down processes or crura, which give off all the common nerves of voluntary motion, etc. I establish thus a kind of circulation, as it were. In this enquiry I describe many new connections. The whole opens up in a new and simple light; the nerves take a simple arrangement; the parts have appropriate nerves; and the whole accords with the phenomena of the pathology, and is supported by interesting views."

Up to the beginning of the nineteenth century there was no physiology of the nervous system properly speaking. Alexander Monro had discovered the ganglions on the posterior roots of the spinal nerves and not on the anterior. Santorini and Wrisberg had noted the two roots of the fifth pair. Pa-

[7] We have a delightful bit showing Roux's affection as well as admiration for Sir Charles in a letter from George J. Bell, Jr., who accompanied him to Italy. He writes to his father from Paris, May 21, 1840: "The way in which Roux and Petit received him was most amusing. When he put his card into his hand it was, 'Ah! Sharley Bell! C'est lui-même!' upon which all the students were gathered round, and the ward resounded with 'Sharley Bell.' He was, of course, much pleased."

letta, tracing the anterior root of the fifth pair to the muscles of the jaw, conceived it therefore to be a muscular nerve, yet it did not seem to lead him to any idea of the function of the larger sensory root.

Scarpa got no further than the question: "Is the posterior root a proper and peculiar kind of nerve, belonging exclusively to the spinal marrow, while the anterior root is a cerebral nerve?"

There was a generally accepted hypothesis that there was a nervous fluid circulating along the nerves, indifferently one way or the other, acting both for motion and sensation. Haller, after a long dissertation, concluded: "But I know not a nerve which has sensation without also producing motion." Bichat seems to have gone further when he recognized the sympathetic system, and which he called the ganglionic system, as a distinct system for vegetative life, with the cerebro-spinal system for the animal life of motion and sensation.

Thus advanced as the anatomy of the nervous system was there was no physiology in step with it until the genius of Bell discovered it. And I cannot in a way but look upon this discovery as greater than that of the circulation of the blood, for while Harvey had something more than mere whisperings of the truth to help him, Bell had nothing but his own great industry in dissection and anatomical knowledge, and patient investigation. But there was his genius which made for him the step from structure to function so easy and so natural. He wrote:

"The view which I have taken of the nerves has not been the result of hasty and premature conjecture, but of patient investigation. From the first year of my delivering lectures, my demonstrations of the brain were given in a manner not then common; and to this peculiarity in the manner in which I looked on the connections of the brain, I trace the origin of opinions different from those hitherto entertained. By the time I began to lecture in Windmill Street I was enabled to follow, in my demonstrations of the nerves, an arrangement which has given a new interest to the subject, and which, by imperceptible degrees and improvements from year to year, during every succeeding course of demonstration, has at length developed the comprehensive system which I have now to present to the reader.

"The steps by which I have cautiously advanced have been observed only by my older and more diligent pupils; who, becoming interested in the subject, have returned during successive years, when it was under consideration, to hear how I continued to prosecute it. They have seen the system gradually developed, and have heard me announcing the desiderata as the inquiry proceeded, and explaining the difficulties; and they have seen how the points which were in one season the most obscure, have by diligent investigation become those of the very highest interest in succeeding courses."

In the whole range of our science I know of no discovery which was the fruit of more patient investigation, I know of no better example of genius as an infinite capacity for taking pains.

Bell's physiology of the nervous system was finally given to the world in six papers presented to the Royal Society from the years 1821 to 1829, as follows: "On the Nerves," read July 12, 1821; a second paper, "On the Nerves of Respiration," May 2, 1822; a paper, "On the Motions of the Eye, etc.," March 20, 1823; second part of the paper, "On the Nerves of the Orbit," January 19, 1823; "On the Nervous Circle Which Connects the Voluntary Muscles with the Brain," February 16, 1826; and a paper, "On the Nerves of the Face," read May 28, 1829.

Briefly stated, Bell's new physiology consisted in the following propositions: He divided the nerves into those of the special senses, namely, smelling, seeing, hearing and tasting; the nerves of general sensation; the nerves of voluntary motion; those which have to do especially with the motions of respiration; and lastly the nerves constituting the sympathetic system, "which seem to unite the body into a whole, in the performance of the functions of nutrition, growth and decay, and whatever is directly necessary to animal existence."

That "the nerves are sometimes separate; sometimes bound together; but they do not in any way interfere with or partake of each other's influence."

That "the key to the system will be found in the simple proposition, that each filament or track of nervous matter has its peculiar endowment independently of the others which are bound up along with it; and that it continues to have the same endowment throughout its whole length."

That "a simple nerve is where the threads or *funiculi* which form its root arise in a line or sequence from the brain or spinal marrow. A compound nerve is where the threads forming the roots arise in double rows, and each row from a different column or tract of nervous matter; for example, the ninth nerve is simple; a spinal nerve is compound."

That "wherever we trace nerves of motion we find that, before entering the muscles, they interchange branches, and form an intricate mass of nerves, or what is termed a plexus. The plexus is intricate in proportion to the number of muscles to be supplied, and the variety of combinations into which the muscles enter."

That "taking the spinal marrow as a whole, its offices are of a double order. First, in relation to the brain; secondly, as having powers emanating from itself, or independent of the brain."[8]

That "it is not determined whether the cineritious matter visible in the section of the spinal marrow belongs to the columns which have reference to the brain, or are distinct organs and new sources of power."[9]

That "the anterior column of each lateral division of the spinal marrow is for motion; the posterior column is for sensation; and the middle one is for respiration. The two former extend up into the brain, and are dispersed or lost in it; for their functions stand related to the sensorium: but the latter stops short in the medulla oblongata, being in function independent of reason, and capable of its office independently of the brain, or when separated from it."

That "an injury to the brain, sufficient to destroy sensation and volition, leaves the spinal marrow in possession of its function, and commanding the actions of respiration."

It is interesting to see how he supplemented his anatomical knowledge by experimentation on living animals, and how repugnant any vivisection was to him on account of his sympathetic nature. Most of his experiments and demonstrations were made by his faithful assistant and brother-in-law, John Shaw:

"After delaying long on account of the unpleasant nature of the

[8] This, I think, is the first intimation we have of the function of reflex action.

[9] Note how careful he is in his assertions.

operation, I opened the spinal canal of a rabbit and cut the posterior roots of the nerves of the lower extremity; the creature still crawled, but I was deterred from repeating the operation by the protracted cruelty of the dissection. I reflected that an experiment would be satisfactory if done on an animal recently knocked down and insensible; that whilst I experimented on a living animal, there might be a trembling or action excited in the muscles by touching a sensitive nerve, which motion it would be difficult to distinguish from that produced more immediately through the influence of the motor nerves. A rabbit was struck behind the ear, so as to deprive it of sensibility by the concussion, and I then exposed the spinal marrow. On irritating the posterior roots of the nerve, I could perceive no motion consequent in any part of the muscular frame; but on irritating the anterior roots of the nerve, at each touch of the forceps there was a corresponding motion of the muscles to which the nerve was distributed. Every touch of the probe or needle on the threads of this root was attended with a muscular motion as distinct as the motion produced by touching the keys of a harpsichord. These experiments satisfied me that the different roots and different columns from whence these roots arose were devoted to distinct offices, and that these notions drawn from the anatomy were correct."

Still resting on his anatomy, he asked himself the question: If I follow the anterior column up into the brain, shall I find the nerves arising from it motor nerves? He traces the anterior column into the corpus pyramidale, and finds there the origin of the ninth nerve (the hypoglossal of our nomenclature), the motor nerve of the tongue.

"Following up the corpus pyramidale, we find issuing from it the sixth nerve, a muscular nerve of the eye. Still following up the *tractus motorius* through the *pons varolii*, we come to the roots of the third nerve, the motor nerve of the eye. *Thus all the nerves arising in this line from the crus cerebri to the cauda equina are muscular nerves.*"

To combat the prevailing opinion that ganglions were intended to cut off sensation, he cut the sensory root of the fifth pair in an ass, destroying the sensibility in all the parts supplied by the nerve. He then cut the nerve of the seventh pair without affecting the sensibility.

"By pursuing the inquiry, it was found that a ganglionic nerve is the sole organ of sensation in the head and face: ganglions were therefore no hindrance to sensation; and thus my opinion was confirmed, that the ganglionic roots of the spinal nerves were the fasces and funiculi for sensation."

Finding a portion of the fifth nerve which did not enter the ganglion, he argued, comparing the fifth pair with the spinal nerves, that this was its motor root. To confirm this he made the following experiment:

"The nerve of the fifth pair was exposed at its root in an ass, the moment the animal was killed; and on irritating the nerve, the muscles of the jaw acted, and the jaw closed with a snap. On dividing the root of the nerve in a living animal, the jaw fell relaxed."

To show his subtile analysis he asked himself the question: If the origin of the fifth nerve is distant from the termination of the column of the cord for respiration, how are the features to be moved in sympathy with the lungs and with the respiratory actions of the breast, neck and throat? And he found that this was effected through the portio dura, a nerve of very distinct origin and different course. He was thus the first to clinically differentiate the facial paralysis due to disease or injury of the portio dura. Many who came to him fearing deep brain trouble were sent away happy with his assurance of its superficial and innocent nature. There are several interesting clinical cases recorded in the appendix to "The Nervous System of the Human Body."

Next in importance to his discovery of the motor and sensory nerves is his paper on the nerves of respiration, and his conception of this function. Only a great anatomist and a genius could have taken the breadth of view and could have based it upon such accurate anatomical details. He had early taken this view in his Anatomy of Expression when he studied the facial expressions with the muscular and respiratory movements in connection with the different emotions. Under the respiratory movements he included the movements of the facial muscles in all the facial expressions, the movements of the nose, lips, soft palate, larynx, chest, diaphragm, and what we know to-day as the auxiliary muscles of labored respiration. Having located the motor nerves in the anterior column, the sensory in the posterior column, and the "nerves of respiration" in what he called the "respiratory column," he was led to give to this lateral column a function as distinctive. The mistake he made in locating the respiratory function in the lateral column of the medulla, based on the origins of the portio dura, the glossopharyngeal, the pneumogastric and the spinal accessory, making the column the distinctive one for respiration the entire length of the spinal cord, and even, in his imagination, continuing it up as high as the origin of the motor oculi, was a very natural mistake, when considered with his discovery of the anterior and posterior roots of the spinal nerves in their relations with the anterior and posterior columns. And mistaken as he was, his conception of the great function stands to-day as it was then conceived. The only mistakes he made with the cranial nerves were with the glossopharyngeal and pneumogastric which he regarded as wholly respiratory and muscular. Respiratory in a certain way they are, but he failed to recognize their sensory functions. With these exceptions, the cranial nerves, in broad outline, as he elaborated them, stand to-day.[10]

[10] Sir Charles Bell's conception and classification of the cranial nerves is in wonderful accord with the most recent researches of His, based upon microscopic and embryological studies. Sir Charles saw plainly that the fifth pair was in type a spinal nerve with its motor and sensory root. A spinal nerve with its two distinct roots was the standard, the typical compound nerve, which he called "regular," in contra-distinction to those cranial nerves which apparently had but one root, motor or sensory, or which supplied special sense organs, or the organs of respiration. These he called "irregular" nerves as deviating more or less from the spinal type. Recent researches must still sanction this division into regular and irregular nerves, although the latter have been shown to be less irregular than the gross anatomy would indicate. For example, the *pars intermedia* of Wrisberg seems in all probability the afferent root of the facial, while the glosso-pharyngeal and par vagum, classed as primarily sensory, have also their efferent roots and efferent ganglia. And most interesting of all, the ganglion of Froriep, a transitory collection of nerve cells representing in a rudimentary condition the afferent

In the great intricacy of the subject it is wonderful, indeed, that he made such few mistakes. His conception of the portio dura, glossopharyngeal, pneumogastric and spinal accessory, as functionally combined, basing his conception on the fact that these four nerves came out from the same column in series, broadly speaking, holds still. Modern research has only elaborated the conception. There is something very beautiful in the way he worked out his whole idea of respiration. The movements of the facial muscles, of the wings of the nose and lips, of the soft palate, glottis, and larynx, of the chest and diaphragm, of the auxiliary muscles of labored respiration, and the muscular movements in connection with sniffing, coughing, crying, laughing and vomiting, he brought into correlation with his respiratory nerves. He called the portio dura the respiratory nerve of the face, the spinal accessory,[11] the superior respiratory nerve, and the posterior thoracic going to the serratus magnus, the external respiratory nerve. The greatness of the work can only be realized when compared with what was known in his day, or rather not known, of the physiology of the nervous system.[12]

In his paper before the Royal Society, "On the Nervous Circle which connects the Voluntary Muscles with the Brain," he showed that "Between the brain and the muscles there is a circle of nerves; one nerve conveys the influence from the brain to the muscle. Another gives the sense of the condition of the muscle to the brain." In his dissections he had traced both sensory and motor nerves to the muscles, and his intuitive genius saw the necessity of a muscular sense. "If a rope dancer measure his steps by the eye, yet on the other hand a blindman can balance his body. In standing, walking and running, every effort of the voluntary power which gives motion to the body, is directed by a sense of the condition of the muscles: and without this sense we could not regulate their actions." It took a genius to see that and make it the science of to-day, one hundred years later.

In his papers on the motions of the eye and the nerves of the orbit we see the same careful and thorough anatomist and acute observer. He was so great and far-reaching as an anatomist and so quick and subtile in his deductions of function from structure that his anatomy had become his all in all, and from anatomy to physiology was but one easy step. This faculty, combined with a tenderness of heart and sympathetic nature generally, made vivisection almost as unnecessary as it was positively loathsome to him. Had he had anæsthesia at his command he would undoubtedly have made more experiments in confirmation of his views and as a source of public demonstration in his lectures; and yet one must feel that nothing could have shaken his faith in the intuitions which came to him from his beloved anatomy. I do not know whether he has been quoted by the anti-vivisectionists of to-day, but surely the following concluding sentences from his paper on the nerves of the orbit is a remarkable statement in support of that cult:

". . . . In the animal body the parts present distinct textures, and are laid in a natural and perfect order; it is necessary only to trace the tubes, or to observe the symmetrical order of the nervous cords, that we may discover their respective uses; the motions, whether of the solid or fluid parts, are so regular and uniform, that the whole offers a subject for observation and induction. Anatomy is already looked upon with prejudice by the thoughtless and ignorant: let not its professors unnecessarily incur the censures of the humane. Experiments have never been the means of discovery; and a survey of what has been attempted of late years in physiology will prove that the opening of living animals has done more to perpetuate error than to confirm the just views taken from the study of anatomy and natural motions.

"In a foreign review of my former papers the results have been considered as a further proof in favor of experiments. They are, on the contrary, deductions from anatomy; and I have had recourse to experiments, not to form my own opinions, but to impress them upon others. It must be my apology, that my utmost efforts of persuasion were lost, while I urged my statements on the grounds of anatomy alone. I have made few experiments; they have been simple and easily performed; and I hope are decisive."

Sir Charles's vision was somewhat obscured by his own brilliancy. He failed to see that investigators of lesser powers might need the help which he could dispense with; and he also failed to see that great as his debt was to anatomy and to his own genius, experimentation was still the final crucial test. The protest against vivisection had this value, at least, that it led to a more restricted use of the privilege, limiting it to those best qualified to use it, and under certain conditions only. The advent of anæsthesia has much simplified the problem. The new science of biology, as of course every biologist knows, is largely based on intelligent experimentation. It was undoubtedly against the French school that Bell's protest

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nucleus of the hypoglossal, a typical motor nerve. So closely has nature held to the type.

Sir Charles's classification of the motor cranial nerves into motor proper and respiratory coincides with the classification of His into the motor nerves arising from the mesial area of the basal lamina of the primitive brain vesicle, and the motor nerves of the lateral area of the basal lamina, with the exception only of the motor root of the fifth pair which His includes with Sir Charles's "respiratory nerves."

[11] In this connection Sir Charles Bell quotes Lobstein, a contemporary of his, professor of anatomy at Strassburg, who, in a dissertation on the spinal accessory, finding it difficult to account for the *nervous fluid* coming by a double passage to the muscle, and unable to discover its true function, made the prediction: "*Veniet forsan tempus quo ista quæ nunc latent, dies extrahat* (sic) *et longioris ævi diligentia.*" He was unaware that already the day and the diligence of his own age had discovered the secret, or a large part of it. These Latin words he consciously or unconsciously picked out of his memory from Cicero, who first wrote them, and in an additional sentence elaborated the thought. They seemed to me an apt motto for this poper.

[12] It is strange, perhaps, in his broad conception of the function of respiration that he says nothing of the sensory side of the function, the *besoin de respirer*, especially as he saw so clearly the muscular sense with the voluntary muscles. All his thoughts and anatomical researches were directed to the motor nerves supplying the respiratory muscles. Even the glosso-pharyngeal and par vagum were motor nerves to him. His error came from the confidence he had in his "respiratory column" of the cord. If the portio dura and the spinal accessory came out from the same groove in the cord and were motor respiratory nerves, surely the two intervening nerves coming out from the same groove were also respiratory motor nerves.

was directed. His contemporary in France was Magendie, who was an ardent vivisectionist, whose work on physiology was based on experiments on living animals. What one accomplished by anatomy and pure genius, the other beat out laboriously by painful and persistent experimentation, yet missing after all the great solution of the problem.

In 1809, to show his interest in surgery, and at a time when he was still absorbed in his anatomical studies, he went down to Portsmouth to study gun-shot injuries in the wounded from the battle of Corunna. He made many fine drawings and paintings of the more interesting cases. He made at that time his well-known drawing of opisthotonos, from a case of tetanus from gun-shot injury of the skull. It is still copied in our text-books.

On June 3, 1811, he married Marion, second daughter of Charles Shaw, Esq., of Ayr. She was his brother George's sister-in-law. The marriage was a most happy one, though childless. Lady Bell survived her husband many years and reached a great age.

In 1815 he visited the field of Waterloo after the great battle and labored with the French surgeons in the hospitals at Bruxelles in caring for the wounded. In his note-books and letters he has given us some vivid descriptions of his experiences, and in the first volume of Quarterly Reports of Surgical Observations, published in 1816, has introduced some characteristic sketches made at the time.[13]

In 1816, 1817 and 1818 he published a series of Quarterly Reports of Cases of Surgery treated in the Middlesex Hospital, in the Cancer Establishment, and in private practice. In these three volumes we find many interesting clinical cases, giving us glimpses of the methods of the time. The most important feature revealed to me is the constant effort at careful diagnosis, the lesson of all lessons to be learned, the one sure sign of efficiency in our profession.

In his clinical jottings it was easier for him to make a rapid sketch than to write a description. Even while traveling and visiting picture galleries he would make rapid sketches of scenes and pictures as a sort of shorthand record to be afterwards elaborated. His brother John had the same gift and used it in the same way in his profession and while traveling.

In 1821 he published a volume of colored plates illustrating the great operations in surgery. In 1824 he published in book form his papers before the Royal Society under the title of "An Exposition of the Natural System of Nerves of the Human Body." It represents his greatest contribution to science and the real work of his life. It is most interesting reading even to-day, not only for its information, but as an inspiration to all workers in our profession.

In the same year he published "Observations on Injuries of the Spine and of the Thigh Bone," illustrated with very fine plates. It is a beautiful quarto volume of 100 pages, and the only polemical writing of Sir Charles I have come across.

[13] When Baron Larrey visited London he dined with Sir Charles Bell. Lady Bell wrote: "He was very happy, and remained till eleven o'clock looking over the sketches of the wounded at Waterloo, and even recognizing cases there in the French Hospital."

In 1822 he published a treatise on the diseases of the urethra, vesica urinaria, prostate and rectum, an elaboration of a work on the subject published in 1810, entitled, "Letters concerning the Diseases of the Urethra." He argued for deliberate and careful instrumentation of the urethra and for all cutting operations in the perineum, reiterating much that he had already set forth in his System of Surgery. He took great pains to refute John Hunter's idea of a spasmodic stricture of the urethra proper, an opinion which he thought had done much harm in the profession. Bell undoubtedly was right in his position. The followers of Hunter had overlooked strictures which required instrumentation, and had mistaken disorders of the bladder attended by spasm at the neck for urethral troubles. According to Bell, obstruction was mechanical obstruction. John Shaw, his faithful assistant in so much of his work, introduced the opinions of the German and Italian surgeons in support of Bell's position. Even in his earlier work Bell contended that the urethra was an elastic, not a muscular tube, and that any contraction in its caliber was the result of congestion, inflammation or exudation. Modern surgery bears him out in this view.

In 1826 he annotated his brother John's "Principles of Surgery," a large work for that day, in four volumes. He cut out much superfluous matter, long quotations from ancient and obscure Latin writers, condensing the work generally and adding many excellent notes of his own. In this work will be found a most interesting history of the operation of lithotomy. I should regard the chapters on hæmorrhage and aneurism as the most important, and as showing best the surgical qualities of the author and editor.

The work by which Sir Charles Bell is best known to the public in general is "The Hand: Its Mechanism and Vital Endowments as Evincing Design." It was written in 1833 as one of the Bridgewater treatises. He received £1000 for the manuscript. In all his work as an anatomist and physiologist, and especially in his lectures, he was ever eager to show design and intelligence in structure and function, and this design and intelligence meant for him the creative mind of a personal God. Throughout his entire life he showed a deep religious nature, which his studies only tended to deepen. This religious temperament was evidently the basis of those moral and emotional qualities which made his entire life and character so beautiful and so charming in every way. It is shown in his love for his family, in his quite constant cheerfulness and almost boyishness of nature, his strong sympathies, his tenderness of heart, and his love of all the simpler joys of life. It seemed quite natural, therefore, that he should have illustrated and annotated along with Lord Brougham Paley's Natural Theology, published in 1836, a type of religious work which seems now strangely old-fashioned. Still another work, very much in the same line, was his "Animal Mechanics," written for the Society for the Diffusion of Useful Knowledge. It had a large sale. In these books he showed the same care in presenting his facts and in sustaining his argument as in his purely scientific papers.

In 1829 the Royal Society of London awarded to him the

first annual medal given by George IV for discoveries in science. And about this time Magendie wrote to him from France that if he would send him any short account of his work he should have the French prize medal, very much of the same order.

When William IV ascended the throne Charles Bell received the Guelphic Order of Knighthood along with a few other distinguished men, among them Brewster and Herschel.

As a recognition from Germany, the University of Goettingen gave him the degree of Doctor of Medicine, honoris causa. As still further evidence of recognition his alma mater in 1836 offered him the chair of surgery.

He had been in London thirty-two years, during which time he had risen to great distinction as a man of science and had attained a good surgical and consulting practice, and with such men in the field as Sir Astley Cooper, Cline, Abernethy and other hardly lesser lights. This rise to distinction had been rapid. He early established his claim as a great lecturer on anatomy, built up his own private classes in anatomy and surgery, and was recognized as the authority on artistic anatomy. He founded a museum of normal and pathological anatomy, human and comparative, which was second only to John Hunter's. It was bought by the Edinburgh College of Surgeons and placed in the fine hall created for it.

His early connection with the School of Great Windmill Street, where he long lectured on anatomy, and with the Middlesex Hospital, where for twenty-four years he operated and delivered many courses of lectures on anatomy and surgery, added much to his reputation and position.

In 1828, on the founding of University College, Gower Street, he accepted a professorship and gave the opening lecture.[14] He became a member of the Royal College of Surgeons, and in 1824 accepted its professorship of anatomy and surgery.

His social qualities seemed quite equal to any position he might attain; yet his busy life did not permit much social life or great intimates. As Lady Bell put it in her reminiscences: "He was too much occupied to form intimacies." He was ever fond of music and the drama, and any notable singer or actor found him at the theater. He was a diner-out on occasions, and himself entertained some notable people.[15]

Even during his early struggling days he was cheerful, buoyant, and confident of his future. Rarely he writes his brother of any depression or sadness, or loneliness—of that sense of *magna civitas, magna solitudo,* as he wandered at times through the streets of "mighty, tumultuous London." He once expressed his feelings in a very subtile way when he wrote:

"I never thoroughly hated London while I could lose myself in it. I had a pleasure in wandering through streets I did not know; but at last it appeared to me to consist of insignificant parts almost infinitely multiplied."

There is a refreshing optimism which will not permit sadness.

"I thought that all was right in the system of the universe—that consistent with our desires and passions was the shortness of our life; and our being liable to suffering and disease—that without this we should have been inanimate, cold, and heartless creatures."

His attitude towards the profession was to be true to himself—true to his moral consciousness and convictions of the right. "Did I ever tell you," he wrote his brother, "I was offered £100 a year for the use of my name? But I thought they would dirty it, so I would not lend it. It was to stick on the first leaf of a journal." And this integrity had also with it a noble independence. In another letter he wrote his brother:

"You tell me to cultivate men; I wish you had said, to be industrious and cultivate a proud spirit of independence. You think of the men you mention as my superiors, and I think you wrong. My object in life is fulfilled as far as my years permit. ——— is only an amicable expectant, who has as yet disappointed the hopes of his friends. He has been creeping into a situation instead of proudly taking his seat. Think better of this, my dear brother, and when you are unsuccessful, or think yourself passed over, it will be a comfort to you to reflect on this as I do. The only virtues in the present state of society are industry and independence. My poverty is sometimes distressing, but only on certain occasions when my character outruns my means."

His ambition was always great, but it was of a high order and free from worldliness. Once he wrote: "I am quite clear that posthumous reputation is an absolute good."

It was his ambition to make discoveries in science and to be a great surgeon; an immense practice with the acquisition of much money he never strove after. He certainly had no time to cultivate practice in any outside way. He wrote his brother:

"You say that no man can rise into great practice without being in company, or, rather, say society. I do not agree with you. Pardon my vanity when I say that my business comes through, and will increase by different means. My patients are now of a proper class, whom I know nothing of. They come from my character, and are retained by finding relief; by being treated with attention and kindness. My means of being known are through my books and pupils. *I retain my consequence by preferring science to practice.*"

And later in life, when his practice had grown much, he wrote:

"But I think this driving after business will prove a poor business, in one sense. It is a wreck of mind. However, I am fast accomplishing that which we all wished and expected by my coming here, but I could as soon give myself an aquiline nose, as pursue practice, and run after patients, as I see some do."

And so, in 1836, after thirty-two years of London, where he had done his great scientific work, where he had built up his

[14] Finding the existing conditions not satisfactory, and at variance with his own ideas of a university, he soon resigned this position.

[15] He was on friendly and sometimes intimate terms with the best in his profession, notably, Sir Astley Cooper, Abernethy, Baillie, and Sir Joseph Banks. He could count among his friends Sydney Smith, Lord Brougham, Lord Jeffrey, Lord Cockburn, Sir Walter Scott, and the poets Campbell and Moore. He entertained Baron Larry, Baron Cuvier, and M. Roux, when they visited London. He was a welcome guest at many country homes of London and Edinburgh.

[16] Italics mine.

museum, where he had attained his surgical and consulting practice, and where he had made acquaintances and friends among the most desirable, he returned to Edinburgh, the city of his birth and of his alma mater, the home of his dearest brother, the haunt of his childhood, and associated with all he held most dear. For six years he was still to labor as professor of surgery in the University, and as a consulting surgeon. In 1837 he published his Institutes of Surgery, full of wisdom and valuable information, and in 1841 a volume of Practical Essays, two of which, on Squinting and on Purgatives, may be specially mentioned.

During the spring of 1840 he visited Italy and made careful artistic and archæological studies, much of which he embodied in a new edition of his Antomy of Expression, which he almost rewrote.

Late in life, even before he left London, he took up fishing as a pastime and became a most enthusiastic fisherman. For one of his temperament and intensity of life he had found it necessary to get away from London's din and toil, and to go out into the woods and fields and by the streams. These trips helped to satisfy his great love of nature and of the country; and much of his best writing was done under the inspiration of sky and woodland. He left in his note-book some essays on fishing which show the joy he got out of it.

He died suddenly at Hallow Park, near Worcester, while on a visit to friends, from angina pectoris, on April 29, 1842, and was buried in the adjoining churchyard.

In studying this great life, while we must admire his genius and all he accomplished, let us dwell even longer on the beauty and strength of his character, the purity of his heart, the simplicity of his whole nature. Not only do we see a genius unobstructed by any perversity of nature, but, on the contrary, a nature which his genius itself had made beautiful and radiant.

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A SPECIAL FUNCTION DISCOVERED IN A GLANDULAR STRUCTURE HITHERTO SUPPOSED TO FORM A PART OF THE PROSTATE GLAND IN RATS AND GUINEA-PIGS.

By George Walker, M. D.,
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In making a series of autopsies upon rats in which I had experimentally removed the prostate gland, I frequently observed a tough elastic coagulum filling the urethra. Search for the cause of this phenomenon disclosed the fact that it was produced by the mixing of the secretion of the seminal vesicles, with the secretion of two small glands adjacent to them.

This coagulation has been observed before and erroneously explained as caused by the mixing of the prostatic secretion with the seminal vesicle secretion. I made a number of very careful dissections of the anterior lobes of the prostate in order to obtain a pure secretion; this I mixed with the seminal vesicle secretion in small and large amounts, but in no case did I get coagulation. When, however, I took the secretion from a small glandular structure adjacent to and lying in the same fascia sheath with the vesicles, and mixed this with the vesicle secretion, coagulation took place immediately. Again, after having taken out the last-mentioned gland, if I then removed the anterior lobe of the prostate and mixed its secretion with that of the vesicle, I frequently got coagulation. This result was undoubtedly due to contamination with the secretion of the other gland, *i. e.*, the secretion had become more or less smeared on the field of operation so that when the prostate was subsequently removed some of the material came along with it.

Literature.—Leydig, in 1850 (as quoted by Rauther), described very accurately the accessory sexual glands of rodents. He affirmed that the prostate was made up of several lobes, all of which did not have an exactly similar structure. But he did not mention anything about the differences in their functions.

Leuckart, in 1853, stated that the secretion of the prostate gland of the guinea-pig coagulated that of the seminal vesicles; he believed that in this way a plug was formed in the outer portion of the vagina which prevented the escape of the semen.

Landwehr, in 1880, observed the same coagulation phenomenon in guinea-pigs, but did not mention the prostate secretion as taking any part in it. He concluded that it was brought about by a ferment in the blood present in the vagina of the guinea-pig following delivery. He does not seem to have taken note of the fact that it occurred even in the absence of blood.

Rauther, in 1903, in a very exhaustive article on the accessory genital glands of rodents and insectivora, confirms the observations of Leydig and gives some accurate drawings of the prostate and vesicles in which are shown the general shape of the different lobes and the character of the epithelium in each. He quotes Leydig as saying that the secretion from the prostate lobe lying near the vesicle is thicker and more turbid than that from the other portions. Rauther does not say anything about any difference in the functions of the lobes.

Camus and Gley, in 1897-1900, observed this phenomenon, and carrying their observations further, found it in mice, rats and other rodents. But despite the fact that their work was more thorough than any that had been done before, they concluded that coagulation was brought about by the secretion of the prostate and do not mention any special glands in the guinea-pig or rat as a causative factor. In hedge-hogs they found that a gland lying well down in the pelvis, not far from the anus, had this property, and that the prostate proper, or

what they designate as the internal prostate, did not possess it. For a further account of their observations see the following article entitled "The Nature of the Secretion of the Vesiculæ Seminales, etc."

Anatomical Description (*Rat*).—The prostate gland is usually but erroneously described as consisting of six lobes (Fig. 1): (a) two posterior sessile structures lying for the most part behind but extending upward on the lateral surfaces of the urethra so that in some cases they nearly encircle that canal; (b) two large anterior pear-shaped pedunculated lobes which stand well up and away from the urethra; and (c) two somewhat elongated club-shaped lobes which lie in the same sheath with the vesicles.

The glandular structure now under consideration consisting of two distinct lobes (Fig. 1), which for want of a better name we shall designate as the coagulating glands, has a different general shape and histological structure from the prostate; it gives rise to a different kind of secretion and has a totally dissimilar function. In the full-grown animal each lobe is from 14 to 18 mm. in length and from 3 to 6 mm. in breadth. It lies in the same fascia sheath with the seminal vesicle and is supplied by the same blood-vessel. The lobules are larger and more transparent than those of the prostate. It is much more villous and the musculature is much thicker. The secretion is thick and tenacious and contains minute flaky particles, while that of the prostate is thinner and more homogeneous. As shown in Fig. 2, the villi are numerous and long, the fibrous framework is compact, and the surrounding muscle, comprising a longitudinal and circular coat, firm and thick. The alveoli, in the non-distended state, present a large number of villi, three or four times as many as those in the prostate, and even when the gland is very much distended these disappear only in part, while in the prostate the inner surface becomes smooth and flattened out.

The cells, as shown in Fig. 4, are strikingly individual, and markedly different from those of the prostate; they are large and very irregularly shaped; in fact I have seen no organ in which the epithelium has such varied forms. In general they are of the cuboid type, but individually they vary greatly. Some are narrow and high, others wedge-shaped, others of the goblet type, some look like dumb-bells, while a few are almost round, with narrow projections reaching down to the basement membrane. The surface of the cellular layer is rendered uneven by clefts here and there between the cells.

The nuclei are situated in the middle or towards the periphery; in the majority of the cells they are nearer the periphery than the center and only very rarely are they found at the base; as a rule, the nuclei are large round or oval, with darkly-stained dots, interspersed among which is a faintly reticulated structure; in other cells the nucleus appears as a large, dense, black spot. In a few it is so faint that on first inspection it seems to be absent. Occasionally a cell is observed which looks as if it had a double nucleus, but this appearance is probably due to the fact that the cells are closely packed together.

The appearance of the protoplasm varies in the different cells; the border is more or less sharply marked out, but in the active stage the secretion in the lumen of the alveolus seems at certain points to be almost continuous with the cellular protoplasm. A very striking feature in the microscopic picture is the number of cells that have large vacuoles, some of which occupy half of the protoplasm. The protoplasm in other cells is light and has almost the appearance of a feathery frame-work. In the majority it is granular and fairly dense, but not so homogeneous as in the prostate; it is usually clearer near the nucleus and denser towards the periphery. Here and there are goblet-shaped masses extending down between the cells; these look like protoplasm, but they have no nucleus and do not reach the basement membrane.

The secretion of this gland, even in very small amount, produces a coagulation when mixed with the seminal vesicle secretion. For the characteristics of this fluid and the general discussion of the coagulation phenomenon the reader is referred to the following article in this number of the Bulletin.

The two anterior lobes of the prostate gland (Fig. 1) are held in place by a fascia extending over the bladder; they have also a special fascia capsule. Each lobe communicates with the urethra by a single duct. In a well-grown animal they are about 15 mm. in length and 8 to 10 mm. in breadth. Their lobules are small and they are not so transparent as those of the coagulating gland. Figure 3 shows a cross-section of one of them. It is made up of a large number of alveoli which are held together by a rather loose connective-tissue frame-work; each of these alveoli is surrounded by a more or less complete circular and longitudinal muscular coat. In the non-distended state the lumen shows a number of villous projections, but when full of secretion these villi disappear and the surface is smoothed out.

The cells (Fig. 5) are arranged in one layer. They rest directly on a very delicate basement membrane; they are cuboidal; their periphery is in some instances smooth, in others it is broken so that it is hard to differentiate between the actual boundary of the cell and the secretion in the lumen.

The nucleus is situated near the base; it is round or oval, is moderately large, in some cells very light and in others very deeply stained.

The protoplasm varies with the stage of activity. During secretion it is very granular and studded with very minute particles; these are denser towards the periphery. Occasionally light places are seen almost like vacuoles, but these are not nearly so prominent as in the other gland.

The secretion is thin, clear or slightly cloudy and alkaline in reaction. It contains a large amount of inorganic material composed mainly of chlorides together with a considerable proteid constituent. *This secretion does not produce any coagulation when mixed with the fluid from the seminal vesicles.*

The posterior lobes, although in general of a different shape and emptied by several ducts, have a similar histological structure and their secretion is the same as that from the anterior lobes; presumably, therefore, their functions are identical.

The seminal vesicles will be described briefly in order to make clearer their relationship to the foregoing. They consist of two large alveolated sacs; each of these usually has only

one chamber, but occasionally partitions divide the vesicle into separate compartments.

The epithelium is cuboidal and is arranged in one layer; the nuclei are situated near the base; they are oval or round and stain more or less densely. The protoplasm is granular and resembles that of the prostate more than that of the coagulating gland.

The secretion is white and has the consistence of a thick cream. After being allowed to stand it becomes thicker and is like a soft gelatine. As before stated, it coagulates on being mixed with the secretion from the coagulating gland.

Anatomical Description (*Guinea-pig*).—The organs of the guinea-pig (Fig. 6) have a different shape from those of the rat. This difference is particularly marked in the seminal vesicles. A description of the prostate has been given by several investigators; all of the lobes are supposed to belong to the prostate gland and no author has suggested any differentiation in function.

According to my observations the prostate gland consists of two posterior sessile lobes, which correspond to those of the rat, and two rather thin anterior pear-shaped pedunculated leaf-like lobes, which are similar to but not quite so large as those of the rat. The other lobes, which have hitherto been considered as part of the prostate gland, lie near the vesiculæ seminales and correspond to what I have called the coagulating gland in the rat.

The coagulating glands (Fig. 6) are situated very close to the base of the seminal vesicles; in fact intimately hug them. This structure (Fig. 7) has a much denser muscular and fibrous framework than the prostate proper; the tubules are fewer, the lumina of the alveoli larger, and the villi much more numerous. Toward the apex of each lobe the alveoli are separate, but they converge toward the base and empty into a single duct.

The epithelium is arranged in one layer. The cells are regular, of the columnar type; their nuclei oval or rounded; they stain moderately deeply and are situated for the most part near the base of the cell. Their protoplasm is evenly granular and not at all vacuolated. These cells are somewhat different from those in the corresponding gland of the rat and are more like those of the prostate of the rat.

The secretion from this glandular structure is viscid and clear. When it is mixed, even in very small proportions, with the seminal vesicle fluid of the guinea-pig or the rat, an immediate and very pronounced coagulation occurs.

The anterior lobes of the prostate (Fig. 8, cross-section) are made up of tubules, which have the same general shape as those in the rat, but are not so numerous, are smaller and the fibrous structure holding them together is denser. The muscular arrangement is the same. In the empty state the villi are very apparent, but these become pressed out and the surface becomes smooth when the lumen is distended.

The epithelium is arranged in one layer. The cells are columnar and rather tall; their periphery is even. The nuclei are round or oval, and they are situated, particularly in the high cells, nearly in the middle. The protoplasm is evenly granular, does not show any vacuoles, in places is slightly reticulated and towards the top of the cell is more dense.

Each of these anterior lobes communicates with the urethra by a single duct.

The secretion consists of a thin turbid fluid with a slightly alkaline reaction. It does not produce any coagulation of the seminal vesicle fluid, no matter in what proportion it is mixed with it.

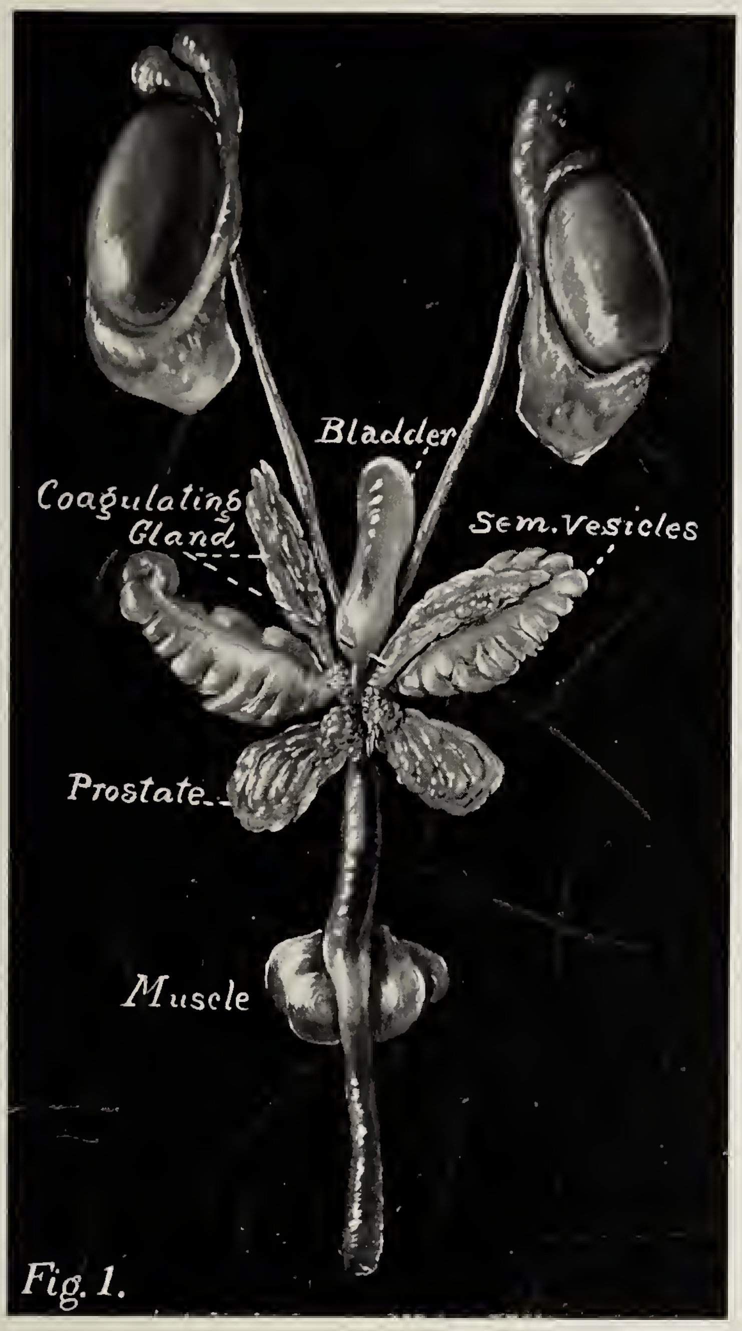
The *posterior lobes* have the same histological structure and the same secretion as are found in the anterior; they empty into the floor of the urethra through several ducts.

The seminal vesicles are free in the peritoneal cavity except for their attachment at the urethral end. They are two delicate worm-like structures about 10 cm. in length and 6 mm. in diameter at their base; they taper from the urethral to the distal end. The outside is smooth and is covered by a fascia sheath which supports the blood-vessels. Each vesicle consists of a single chamber. The inner surface, even when the lumen is distended, presents a number of very delicate and branched villi. There are two muscular coats, a circular and a longitudinal. The epithelium is one layer in thickness; the cells are slender, tall and very similar to those seen in the rat. Each vesicle empties by a single duct into the urethra.

The secretion consists of a clear, tenacious material which during life is fluid, but, within a few minutes after death, assumes the consistence of a prepared gelatine. When mixed with a small portion of its own coagulating gland secretion or with that of the rat, it is immediately coagulated.

The Relationship between the Ducts of the Prostate, Coagulating Gland and Seminal Vesicles of the Rat.—By carefully prepared serial sections I have studied the ducts leading from the various glandular structures. All of these empty into the floor of the urethra near a point corresponding to the veru montanum. The ducts from the coagulating glands pass along with those from the seminal vesicles and empty on the floor of the urethra just behind them. The seminal vesicle ducts then empty just in front of the coagulating gland ducts. The ducts from the large anterior lobes pass down and become so intimately mingled with those from the posterior lobes that it is difficult to say exactly where they terminate. I am fairly positive, however, that they empty in front of those from the coagulating glands and seminal vesicles. The ducts from the posterior lobes, eight or ten in number, have separate openings and these are scattered before and behind the openings of the seminal vesicles and the coagulating glands; for the most part they are in front. The ejaculatory ducts become blended at their mouths with the ducts from the seminal vesicles, but this does not occur until the mucosa of the urethra is reached.

The coagulating gland should not be considered a part of the prostate. From the above description it is clear that the glandular structure in guinea-pigs and rats, which I have designated as the coagulating gland, is not a portion of the prostate and should not, therefore, be so named nor considered. It has a different general shape, a different histological structure and



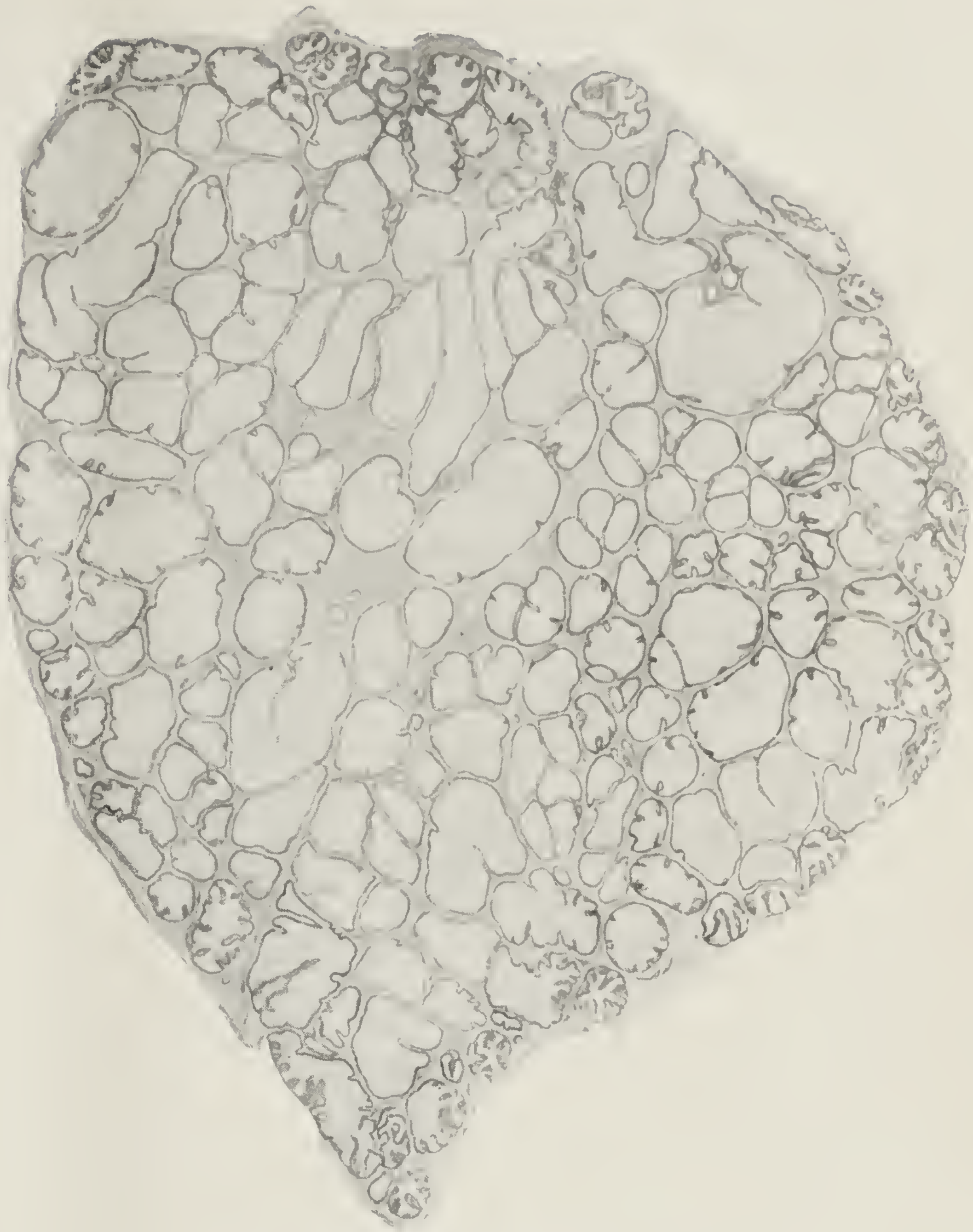


FIG. 3.—Prostate Gland, Rat. × 21¾.

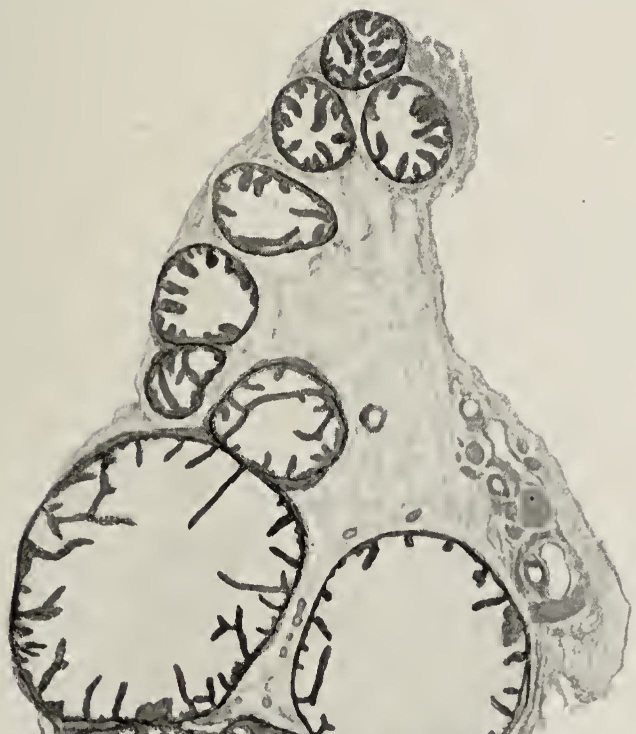


FIG. 2.—Coagulating Gland, Rat. × 19½.

FIG. 4.—Coagulating Gland, Rat. × 460.

FIG. 5.—Prostate Gland, Rat. × 460.

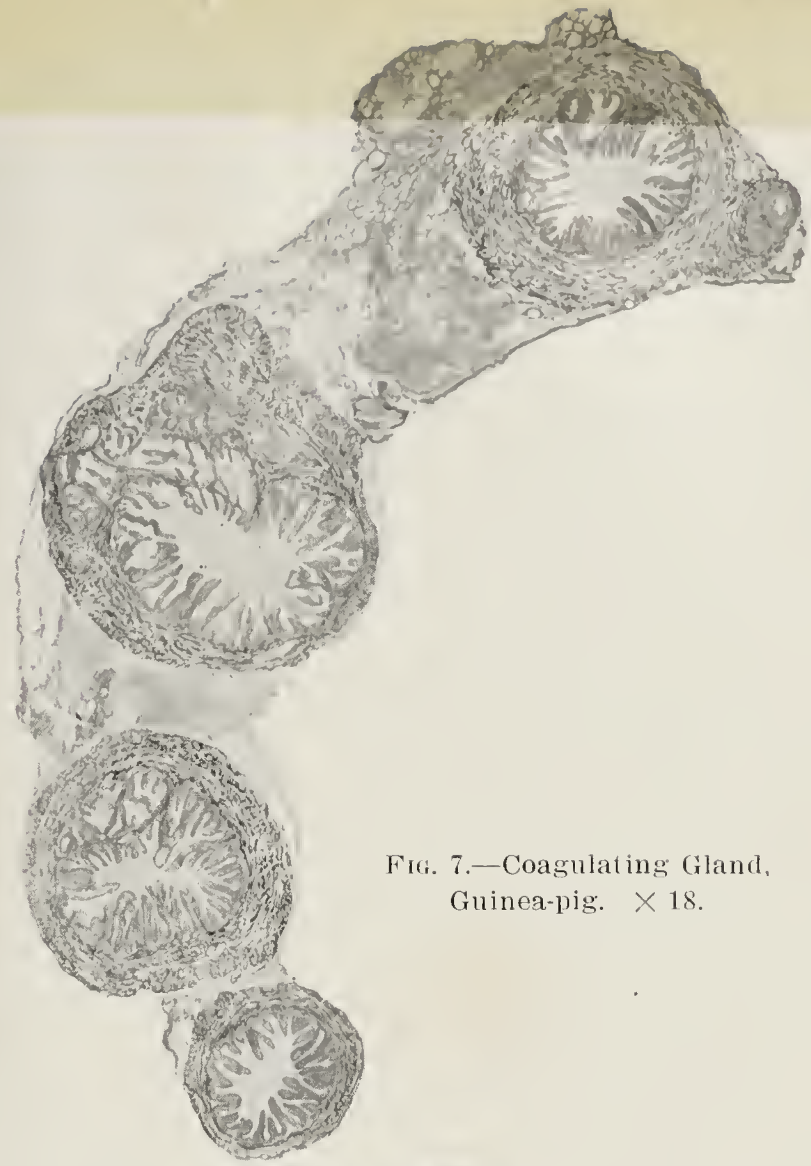


FIG. 7.—Coagulating Gland, Guinea-pig. × 18.

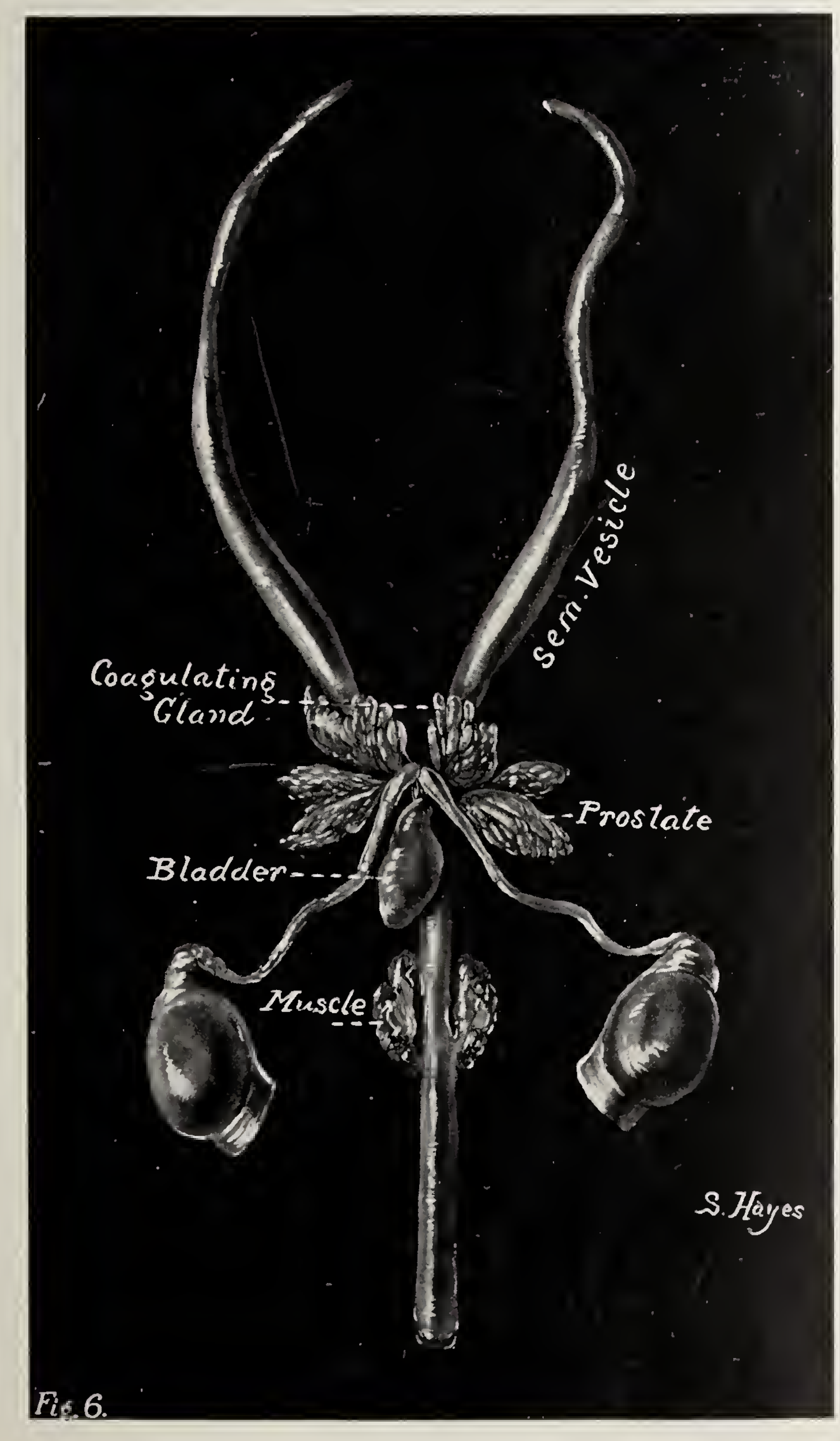


FIG. 8.—Prostate Gland, Guinea-pig. × 16½.

gives rise to a secretion which is physically and chemically unlike the prostatic fluid, and has entirely distinct functions.

The function of the prostate is probably to furnish a secretion in which the spermatozoa can move freely; as they are extruded from the ejaculatory ducts in rats, they are so closely packed together and in such a thick, tenacious material that they can have no practical motility.

The secretion of the prostate furnishes a diluent and perhaps a stimulant; in the absence of this gland its place may in part be taken by Cowper's gland and the urethral glands. The coagulating gland furnishes a secretion which coagulates the seminal vesicle secretion, and by this means a plug is formed in the outer portion of the vagina, which probably prevents the escape of the semen. This gland, therefore, furnishes a fluid which is in every way distinct from that of the prostate.

Does the coagulating gland exist in other animals? Just how extensive is the occurrence of this gland in the animal kingdom I do not know. It is present in rats, guinea-pigs, mice and probably in hedge-hogs. I have failed to find it in rabbits; it is probably not present in the carnivora, for most of them have no seminal vesicles. I have examined bullocks, but was unable to find it and the chemical examination of the seminal vesicle secretion does not indicate that it contains a substance similar to that found in rodents.

In the human subject coagulated particles in the semen suggest the presence of the gland but I have been unable to find it. The normal secretion from a human seminal vesicle is thick and sticky and resembles in physical consistency that of the rat. In the ejaculated fluid one always finds semi-solid and occasionally solid particles. This certainly suggests coagulation, for this lumpy material differs from the normal vesicle secretion and it appears, therefore, that it has been produced at the moment of ejaculation.

It is possible that the human seminal vesicle has a similar function to that of the rat; operating, however, to a much less degree and while not producing a definitely formed coagulation, the vesicle secretion, when mixed, may form a soft coagulum, the purpose of which is to adhere to the walls of the vagina and would tend to prevent the spermatozoa from escaping when the female is in the upright posture. This, of course, in so far as the human subject is concerned, is largely hypothetical, but I trust that I may be able within a short time to make the examination in a sufficiently fresh subject to determine the exact condition.

Summary.

1. The glandular structure lying in the same sheath with the seminal vesicles of the rat and guinea-pig is very different histologically from the prostate and has an entirely distinct function.

2. The secretion from the above gland, which I have designated as the "coagulating gland," coagulates the seminal vesicle secretion when mixed with it.

3. The secretion from the prostate gland does not coagulate the seminal vesicle secretion.

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THE NATURE OF THE SECRETION OF THE VESICULAE SEMINALES AND OF AN ADJACENT GLANDULAR STRUCTURE IN THE RAT AND GUINEA-PIG, WITH SPECIAL REFERENCE TO THE OCCURRENCE OF HISTONE IN THE FORMER.

By George Walker, M. D.,

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Leuckart (1853), from some observations made on guinea-pigs, concluded that when the prostatic secretion was mixed with the seminal vesicle fluid a coagulum was produced.

Landwehr (1880) observed this same coagulation, but apparently did not connect the prostate with the change. He concluded that the vesicle fluid was coagulated by a ferment of the blood which is present in the vagina just after the female has given birth to her young, the male having sexual intercourse with the female very soon after delivery. He thought that the substance in the secretion from the vesicles was akin to fibrinogen.

Camus and Gley (1897-1900) observed the same phenomenon and extended their investigations to rats, mice, hedgehogs and the myopotamus. According to these authors the secretion from the prostate gland of the rat or guinea-pig coagulates the secretion from the seminal vesicles in the respective animals and also that the secretion from the prostate of one would coagulate the vesicle secretion of the other.

They noticed that only a very small quantity of the prostatic fluid was necessary to effect this coagulation and from this fact and other experiments they concluded that the fluid contained a ferment which they called "vesiculase." This

substance is destroyed by a temperature of 100° C., but when evaporated to dryness it stands 140° C., without being damaged. In the hedge-hog the gland which secretes this fluid is situated low in the pelvis and probably corresponds to Cowper's gland. The prostate proper, according to them, in this animal does not contain a coagulating agent.

These authors did not differentiate in rats and guinea-pigs between the prostate and the peculiar gland which produces this unusual secretion; at least, in none of their articles do they mention any special organ, but speak solely of the secretion of the prostate.

My own observations have led me to conclude that:

(1) The prostatic secretion does not produce any coagulation at all when mixed with the seminal vesicle secretion, provided that care is taken to prevent contamination from a neighboring gland.

(2) The material which produces the coagulation comes from a glandular structure adjacent to the seminal vesicles.

(3) The prostate gland and the gland above mentioned are two entirely different structures with separate and distinct functions. My reasons have been given in full in the accompanying article entitled "A Special Function Discovered in a Glandular Structure," etc.

(4) The substance found in the seminal vesicle secretion most probably belongs to the group of histones.* The data upon which this conclusion is based will be set forth in the following pages.

Miescher, in 1878, separated a substance from the spermatozoa of the salmon which he called protamine. Kossel later studied this body and determined that it was the simplest protein substance.

Kossel, in 1884, isolated from the red blood cells of a goose a material which he named *histone*. Since that time he has found this same agent in the spermatozoa of various fish and in the thymus gland of the calf.

Histone, according to Kossel, has a somewhat more complicated molecule than protamine. He places it, therefore, in his protein classification next in line above protamine. These two substances have numerous properties in common.

The characteristic reactions of the histones are the following:

(1) They are not coagulated by heat unless there is present a definite quantity of salts, particularly of sodium chloride.

(2) They are precipitated by ammonia in the presence of ammonium salts and, under certain conditions, by ammonia in the absence of the salts.

(3) They are thrown down by nitric acid, the precipitate clearing up on boiling and reappearing on cooling.

(4) According to the observations of Ivor Bang they precipitate other proteins, particularly egg albumen, blood serum and casein.

(5) They are thrown out of neutral solutions by the alkaloidal reagents, sodium phosphotungstate, sodium phosphomolybdate and potassium ferrocyanide (Bang).

(6) They have a nitrogen content varying from 14 to 19 per cent.

(7) When hydrolyzed they break up into diamino-acids, notably the three hexone bases, lysin, histidin and arginin.

(8) They contain sulphur.

The protamines differ from the above in the following respects:

(1) They are not coagulated by heat.

(2) They are more strongly basic.

(3) They are precipitated by the alkaloidal reagents from an alkaline medium.

(4) They do not contain sulphur.

(5) They give a less pronounced reaction to the biuret and to the xanthoprotein reagents.

Seminal Vesicle Secretion (Rat).

The vesicle secretion is a white fluid having about the consistence of a thick cream. It is slightly alkaline, has no odor, and, after the death of the animal, becomes thicker and finally almost gelatinizes.

Relationship of the Vesicle Secretion to that of the Other Glands.—When a very small quantity of the secretion of the adjacent gland, which we shall here call the "coagulating gland" is mixed with the natural vesicle secretion, an immediate coagulation occurs. If this secretion is added to the salt solution vesicle extract, a coagulation soon takes place to such an extent that the whole fluid seems to become solid.

If the prostatic secretion is taken out with great care so as to avoid any possible contamination with that of the other gland, there is no coagulation when it is mixed with the natural vesicle secretion, nor is there any coagulation of the salt solution extract even when the prostatic secretion is added in large amount and allowed to stand for a number of hours.

Determination of Weight of Dried Substance and Ash.—The material from five rats was very carefully taken out so as to avoid contamination. This was weighed and kept in an oven for two days at a temperature of 70° C.; for two days at 80° C.; for two days at 100° C., and finally for one day at 110° C. Weighings were made at intervals and the substance was dried until the weights became constant. The material did not show any evidence of overheating. After the final weighing the dried substance was incinerated.

The weights were as follows:

Weight of material from 5 rats.....	3.203	gm.
Weight of material after drying ...	.798	gm.
Weight of material after combustion	.0114	gm.

* For those readers who have not familiarized themselves with the recent classification and nomenclature of proteins, a short synopsis is given. The following has been recently adopted by the American Physiological and Biological Chemical Societies:

Simple Proteins.	Conjugated Proteins.	Derived Proteins.
(a) Albumins.	(a) Nucleoproteins.	(a) Proteans.
(b) Globulins.	(b) Glycoproteins.	(b) Metaproteins.
(c) Glutelins.	(c) Phosphoproteins.	(c) Coagulated proteins.
(d) Alcohol-soluble proteins.	(d) Hæmoglobins.	(d) Proteoses.
(e) Albuminoids.	(e) Lecithoproteins.	(e) Peptones.
(f) Histones.		(f) Peptides.
(g) Protamines.		

Solubility.—The following agents were employed to dissolve the material: Distilled water; 0.6 per cent sodium chloride solution; 0.5 per cent hydrochloric acid solution; 0.5 per cent acetic acid solution; and 0.5 per cent sodium hydrate solution.

Distilled Water.—When the vesicle secretion was mixed with distilled water, the fluid remained cloudy and could not be filtered nor centrifuged, nor did it separate on standing. One could not, therefore, in this manner determine anything about the solubility. Accordingly a solution of the vesicle material in salt solution was dialyzed until it was salt free, or at least so nearly so that the surrounding fluid gave no reaction to nitrate of silver. The material in the dialyzer was still in solution, no precipitate having occurred, and it gave the test characteristics for the vesicle secretion. I concluded, therefore, that the material is soluble in distilled water.

A second test was made in the following manner:

The salt solution extract was precipitated with alcohol and the precipitate washed several times with dilute alcohol. It was then evaporated to dryness and taken up in distilled water. This solution was filtered and the clear filtrate gave the characteristic reactions. These two experiments prove conclusively that distilled water is a solvent in the absence of any salts.

Other Solvents.—The acetic and hydrochloric acid solutions apparently dissolve more than the salt solution. Sodium hydrate takes up larger quantities than either.

Salt Solution.—When the material was mixed with a 0.6 per cent sodium chloride solution a thick emulsion was produced. This filtered with difficulty, but on standing, or being carefully centrifuged, a clear supernatant fluid could be obtained which was found to be rich in protein. A sodium chloride solution was therefore adopted for the experimental work.

Reactions of the Salt Solution Extract.—In order to determine the amount of the solid portion of the vesicle secretion which is soluble in a 0.6 per cent solution of sodium chloride I employed the following method:

I prepared an accurate solution of sodium chloride, and with this I made a saturated solution of the vesicle substance. Five cubic centimeters of this fluid were put in a previously weighed dish and weighed. After this, it was evaporated to dryness and then kept in an oven until all the water had been driven off, after which the residue was weighed and the amount of sodium chloride calculated and subtracted. From this it was ascertained that the amount of dried vesicle secretion in the salt solution was 1.39 per cent.

The weights were as follows:

Weight of dish....................	12.4514 gm.
Dish plus saturated solution of substance in salt solution.........	17.3743 gm.
Dish plus dried substance plus dried sodium chloride	12.5500 gm.
12.5500 minus weight of dish equals	.0986 gm.
.0986 minus .03 (NaCl) equals.....	.0686 gm.
Calculating with these figures, then, the amount of dried vesicle secretion in salt solution would be	1.39%

The solution is faintly alkaline. On boiling there is a faint cloud. After the addition of a very small quantity of acetic acid, and then boiling, the fluid remains perfectly clear. With the acids—acetic, hydrochloric and sulphuric, strong and dilute—there is no precipitate. In fact, if there is any turbidity, it disappears on the addition of the acid. With the sodium hydrate solution there is a slight precipitate, which dissolves in an excess. With a 3 per cent sodium chloride solution there is a flocculent precipitate, which is not soluble in an excess. With a half-saturated ammonium sulphate solution there is a dense precipitate; when this is allowed to settle, and ammonium sulphate crystals are added to saturation, there is an additional precipitate formed, but not nearly so heavy as in the first instance.

With a half-saturated magnesium sulphate solution, there is a precipitate, but not as great as with the half-saturated ammonium sulphate solution. On saturation with magnesium sulphate there is an additional precipitation.

When a saturated solution of sodium carbonate is added in equal volume, there is produced a voluminous precipitate, which is not soluble on heating. When a saturated solution of sodium bicarbonate or the crystals are introduced, there is no precipitation, but if acetic acid is added afterwards, a voluminous precipitate is formed. With sodium citrate, sodium phosphate or sodium acetate, a precipitate occurs. With the same potassium salts, a precipitate is produced. With the ammonium salts, precipitation results. With calcium chloride and calcium acetate solutions, there is no precipitation. With magnesium chloride or magnesium acetate there is no precipitation. Mercuric chloride produces a very dense precipitate. Basic lead acetate forms a dense precipitate. Trichloracetic acid gives a heavy white precipitate, which does not change on heating. With alcohol there is a light, very voluminous white precipitate.

Characteristic Reactions.—The following reactions for the secretion from the seminal vesicles of the rat correspond identically with those for histone:

(1) With concentrated nitric acid in the cold a dense precipitate is produced; this entirely clears up on heating, so that the solution is practically clear; on cooling the precipitate reappears.

(2) When ammonium hydrate is added, there is produced a precipitate. If the ammonia is added very slowly, a precipitate is formed, which sometimes is soluble in excess, but more often not. If a quantity of ammonia—I mean by this, as much ammonia as material—is dashed in, there is formed a momentary precipitate, which entirely dissolves, leaving a clear fluid. If, on the addition of the ammonia, a very small quantity of ammonium chloride is present, there occurs a voluminous precipitate, which is not soluble in excess. If the ammonia is added, so that no precipitation is produced, and then ammonium chloride crystals are dropped in, a voluminous and permanent precipitate is formed. If ammonia is added beyond saturation to a solution of the vesicle fluid containing acetic or hydrochloric acid, a precipitate is immediately formed, which is not soluble in excess. All the ammonia precipitates

are soluble on the addition of acids in excess. The above reactions correspond to those given by Bang, and are somewhat at variance with the characteristics of histone as set forth by the American Chemical Society.

(3) Precipitation by alkaloidal reagents: With a 1 per cent solution of phosphotungstate of sodium, a decided precipitate is produced; this occurs even if the vesicle solution is distinctly alkaline.

With a saturated solution of phosphomolybdate of sodium, both in alkaline and neutral conditions, there is a marked precipitate.

With potassium ferrocyanide, 10 per cent solution, a vesicle secretion, whether neutral or alkaline, gives a distinct precipitate, which partly dissolves on excess of the reagent.

(4) When the vesicle salt solution extract is added to a 1 per cent solution of egg albumen or to blood serum, there is a voluminous precipitate.

The last two reactions, namely, the precipitation by the alkaloidal reagents in a neutral medium and the precipitation of other proteins correspond with Bang's results.

The hydrochloric, acetic and sodium hydrate solutions were each separately tested for the foregoing reactions, and found to correspond except in those particulars which would be influenced by the aforesaid chemical agents. This proved that these agents dissolved the same substance as did the salt solution.

Nitrogen Content.—Two Kjeldahl estimations were made. In the first, 0.8007 gram of the dried material was used; this yielded 15.41 per cent of nitrogen. In the second instance, 0.5912 gram yielded 15.20 per cent.

Sulphur Content.—The material was fused with metallic sodium; this mass was then dissolved in water and potassium nitroprusside solution added; a beautiful purple color was obtained, indicating the presence of sulphur.

Phosphorus Content.—The material was fused with sodium carbonate and sodium chloride. This mass was dissolved in distilled water and treated with ammonium phosphomolybdate. After 12 hours there were some very indefinite yellow crystals on the side of the tube, so tiny that they scarcely could be discerned.

Protein Reactions.—The biuret reaction was quite positive; it gave a very beautiful violet color, with no tinge of red. Millon's reagent produced a typical brown red discoloration. The xanthoprotein reaction was positive in a number of instances.

Dialysis.—With dialyzers made from collodion and proven free from holes, a number of experiments were made. In no instance did any of the material pass through.

Calcium Content.—Several qualitative tests for calcium were made. It was found in only the merest trace; certainly it did not form any appreciable part of the secretion.

Mineral Content.—The mineral substance from 3.2030 grams of the natural vesicle secretion was 0.114 gram.

Hydrolysis.—In order to determine definitely the character of a protein, hydrolysis must be resorted to. It was impossible for me to try this for the reason that as I could obtain such a very small quantity from each rat, it would have taken about a thousand full-grown male rats to supply the required material.

Reactions of the Seminal Vesicle Secretion of the Rat with Extracts of Other Organs (Rat).—The liver, spleen, kidney, lungs, brain, testes and intestines were separately ground up with salt solution. These were placed in separate tubes, allowed to stand and the clear liquid drawn off. A number of small tubes were then partially filled with the vesicle secretion in salt solution; to each of these tubes two drops of the extract from one of the organs were added. That is to say that to one tube, extract of the liver was added; to another, extract of the spleen, and so forth. There was an immediate precipitation, but in none was there any coagulation, even after 12 hours. A small quantity of the gastric juice was also added to one tube; no coagulation occurred. These experiments were done in order to determine whether there is any similar coagulating agent in any other part of the body.

What Amount of Histone is Present?—It will be noticed in all of the foregoing that I have experimented with the whole vesicle secretion. A number of attempts by means of precipitation (ammonia, alcohol) were made to isolate the histone or the allied substance in a pure form, but none of these efforts was satisfactory. I am aware that this failure opens the work to criticism, and regret that it could not be avoided. Histone is most probably present, but the proportion I am not now able to state. Later I shall discuss more fully this question.

Secretion from the Seminal Vesicle (Guinea-pig).

In the living animal the vesicle secretion is fluid; at the moment of death, or very soon after, it becomes thicker, and in a short time assumes the consistency of a soft jelly; it is homogeneous, beautifully transparent, without color and with almost no odor.

When the vesicle secretion is mixed with that of the adjacent gland an immediate coagulation occurs, as in the case of the rat. The coagulated material is tough and elastic. When the vesicle secretion is mixed with the prostate secretion, provided no contamination has occurred, there is no coagulation.

Solubility.—The same solvents which were used for the vesicle secretion of the rat were tried and were found to act in much the same manner for the guinea-pig. The actual amount dissolved was approximately the same, but an exact calculation was not made.

Distilled Water.—The same experiments by dialysis and precipitation were tried and the material was found to be soluble in distilled water.

Characteristic Reactions.—Tests with the material dissolved in 0.6 per cent salt solution gave the following results:

It has a slightly alkaline reaction.

There is not the slightest cloud on boiling, nor is any produced by the addition of acetic acid and then boiling.

Acetic, hydrochloric and sulphuric acids produce no precipitate.

On the addition of an equal volume of a saturated solution

of ammonium sulphate, there is produced a voluminous precipitate. When this is filtered and ammonium sulphate added to saturation, there is a decided cloud.

With a half-saturated solution of magnesium sulphate there is no precipitate; on addition of the salt to saturation, there is formed a moderately heavy white precipitate.

With a half-saturated sodium chloride solution there is no precipitate. On saturation there is a voluminous precipitate.

A half-saturated solution of potassium or sodium acetate produces no precipitate.

With a half-saturated sodium carbonate solution there is no precipitate.

With an equal volume of 95 per cent alcohol there is produced a fine voluminous precipitate.

With an equal volume of a 10 per cent solution of potassium ferrocyanide there is no precipitate.

With an equal volume of a 1 per cent solution of sodium phosphotungstate there is no precipitate.

With an equal volume of a saturated sodium phosphomolybdate solution there is no precipitate.

With a small or large amount of ammonium hydrate, either in the presence or absence of ammonium salts, there is no precipitate.

With a solution of egg albumen there is no cloud.

With guinea-pig or rat blood serum there is no cloud.

When the salt solution extract is acidulated with acetic acid and then sodium phosphotungstate, sodium phosphomolybdate or potassium ferrocyanide is added, an immediate and dense precipitate is formed.

When concentrated nitric acid is added there is formed a dense precipitate, which not only does not clear on heating, but seems to be increased.

From the above it will be seen that the reactions shown by the vesicle secretion of the guinea-pig in some particulars are strikingly different from those in the case of the rat, some of the characteristic ones being absent; viz.:

(1) The behavior of the fluid with nitric acid is very different.

(2) It is not precipitated by ammonia in any way.

(3) It is not precipitated from neutral or alkaline solutions by the alkaloidal reagent.

(4) It does not precipitate other albumins.

Protein Reactions.—The biuret reagent gives a very beautiful purple color, with no tinge of red.

Millon's reagent gives a well-marked and typical color reaction.

The xanthoprotein reaction is typical.

Dialysis.—The material in salt solution was tried in the dialyzer a number of times; in no instance did any pass through.

Nitrogen Content.—Three estimations were made:

No. 1, 0.6206 gram of dried material yielded 16.80 per cent.

No. 2, 0.9214 gram of dried material yielded 17.15 per cent.

No. 3, 0.7060 gram of dried material yielded 17.18 per cent.

Sulphur Content.—From the same test as was made for the rat it was found that sulphur was present.

Phosphorus Content.—The ammonium phosphomolybdate test was applied. A very faint yellow precipitate was obtained, showing the presence of phosphorus, but in very small amount.

Calcium Content.—Calcium was found in very minute quantities—one might say only a trace.

Determination of Amount of Gland Secretion Necessary to Produce Coagulation (Rat).

Experiment 1.—A series of ten very narrow tubes were prepared and into each was put an equal quantity of the vesicle secretion in salt solution. A very fine capillary tube was made and the coagulating gland secretion drawn up to a mark about one inch from the end. This amount was put into tube No. 1, containing the above-mentioned vesicle secretion; into tube No. 2 double the amount; into tube No. 3, three times the amount and so on up to No. 7. An immediate precipitation occurred in all of them, being greatest in the one which had the largest quantity. After ten minutes tubes Nos. 7 and 6 were coagulated. The coagulation time in the other tubes varied from 12 to 45 minutes. At the end of this time all of them showed about the same degree of coagulation.

Into tube No. 8, one-half as much was introduced as in tube No. 1; into No. 9, one-fourth as much; into No. 10, the least quantity which I could manipulate within the tube. No. 8 coagulated after one and one-half hours; No. 9 after about three hours; No. 10 was solid after 12 hours.

Another tube, with the same quantity of vesicle secretion, was prepared; the same capillary tube as was used above was sealed and its lower end moistened for about one inch with the coagulating gland secretion; the material in the tube was stirred well with this. No immediate effect was produced, but after 12 hours there was a complete coagulation.

Experiment 2.—Eight more tubes were selected and 20 drops of the salt solution vesicle extract were poured into each. Then, a dilution of the secretion from the coagulating gland was made with normal salt solution, representing one part of the former to 400 of the latter. One drop of this mixture was put into tube No. 1 (containing the vesicle solution), two drops into tube No. 2, three drops into tube No. 3, and so on up to eight drops in tube No. 8. The tubes were all thoroughly shaken. There was a slight haze produced, but no immediate coagulation. After 10 hours the cloudiness in tubes Nos. 4, 5, 6, 7 and 8 had increased, but the material was still entirely fluid. Supposing that no coagulation would occur, two drops more of the coagulating solution were introduced into each tube. These were observed 8 hours later; 5, 6, 7 and 8 had coagulated completely; 3 and 4 were very clouded; 1 and 2 were moderately clouded. After 24 hours Nos. 3 and 4 had coagulated; after 36 hours Nos. 1 and 2 had coagulated. In tube No. 1, which coagulated after 36 hours, the dilution represented one part of the ferment to 3063 parts of the salt solution extract. Now, if we take this solution as representing 1.39 per cent of the dried vesicle material, we have approximately one part of the glandular secretion to 21,300 parts of the seminal vesicle secretion.

Guinea-pig.—A similar experiment, but not so elaborate, was done for the guinea-pig, and it was found that an exceed-

ingly small quantity, simply a little moisture on a capillary tube, would produce coagulation. With the small amount the action was correspondingly slow.

Relation of the Phenomenon to Blood Coagulation.—Some of the coagulating gland secretion was mixed with a pure solution of fibrinogen obtained from the cat's blood. Not the slightest coagulation occurred, even after ten hours. A solution containing fibrin ferment from the cat's blood was mixed with the vesicle secretion, but no coagulation occurred, even after the lapse of several hours. Fibrinogen solution was prepared from the rat's blood, and the coagulating gland secretion added; no coagulation was produced.

The blood serum of the rat a number of times was added to the vesicle secretion without the slightest effect. If, however, after the coagulating gland had been removed, blood serum, or even a blood smear, was taken from the pelvis, and mixed with the vesicle secretion, a coagulation was produced in a very short while. This test I repeated often enough and under sufficiently varied conditions to prove conclusively that this coagulation was produced by the coagulating gland secretion which had become mixed with the blood in the pelvis. If, in the same animal, I opened the chest and took the blood from that cavity, care being taken not to use the same instruments, there was never the slightest coagulation.

The Effects of Sodium Oxalate and Sodium Citrate.—One part of a 1 per cent sodium oxalate solution was mixed with nine parts of the salt solution of the vesicle material; to this was added the usual amount of coagulating gland secretion; rapid and complete coagulation occurred. One part of a 2 per cent sodium citrate solution was added to an equal volume of the vesicle solution; then the coagulating gland secretion was mixed in; coagulation occurred as usual.

From these two experiments it is seen that the two agents which prevent the coagulation of blood have no retarding influence on the vesicle phenomenon.

The Effect of Other Agents.—One seminal vesicle was taken out, ligated at both ends and placed in a tube, which was kept in boiling water for half an hour. Upon examination the secretion appeared somewhat thinner than before, but there was no hardening. A small quantity of the coagulating gland secretion was added; coagulation occurred precisely as in the fresh material.

The vesicle salt solution was precipitated with alcohol; this precipitate was washed several times with dilute alcohol and evaporated to dryness. The material was then taken up with salt solution and the coagulating secretion of the rat was added. There was some immediate coagulation; this increased after several hours, and finally about one-half of the material had coagulated. In other words, the coagulation compared favorably with that of the fresh material, but was not quite so extensive.

This reaction was tried a second time, a precipitate, which had been standing in alcohol for two weeks, being employed. Immediate coagulation occurred and in a short time the whole became entirely solid, the process resembling in every respect the ordinary phenomenon.

Characteristics of the Secretion of the Coagulating Gland.

The secretion is thick, rather tenacious, distinctly cloudy and has fine particles suspended in it; it is slightly alkaline and has a faint animal odor.

On standing in a small tube for about two hours, a white, rather granular material settles to the bottom, leaving a clear supernatant liquid. When mixed with salt solution, a slight precipitate is produced; this mixture becomes clear on standing, and the clear portion is very active in producing coagulation.

Heating the secretion up to 60° C. produces a slight coagulation, but does not affect the active agent; heating to 70° C. produces more coagulation, but the principle is still active; heating to 75° C. seems to coagulate the whole material, but if this is broken up and added to the vesicle secretion, coagulation occurs; heating to 80° C. destroys the activity entirely.

When alcohol is added to a salt solution extract of the coagulating gland secretion, a precipitate is formed. If this precipitate is washed several times with dilute alcohol, then evaporated to dryness, the residue being taken up in salt solution, and mixed with the vesicle material, coagulation occurs, but it is slower than with the fresh material.

Boiling.—The secretion, in a small glass tube, was placed in boiling water for 20 minutes; it was then taken out, thoroughly broken up, and mixed with a small quantity of trypsin. This was kept at 37.5° C. for eight hours, after which it was tested with the vesicle fluid and found to have lost its coagulating property. This experiment was made on the supposition that possibly the ferment (?) might be caught in the coagulum produced by heat, and that it could be liberated by dissolving the coagulated material.

Regaining the Active Principle.—Some of the vesicle secretion which had been coagulated was crushed into small particles and washed a number of times with distilled water; salt solution was then added and the mixture allowed to stand for one hour. The supernatant liquid was found to produce coagulation, thus showing that the ferment (?) could be regained from the coagulum.

Precipitation Reactions.—The salt solution extract with a half-saturated ammonium sulphate solution produces complete precipitation. A half-saturated sodium chloride solution produces no precipitate; a half-saturated magnesium sulphate solution causes distinct precipitation. Phosphotungstate of soda and potassium ferrocyanide produce no precipitate, unless the solution is acid. Alcohol, 95 per cent, in equal volume, throws down a voluminous precipitate. Ammonium hydrate does not produce any precipitate.

Characteristics of the Prostatic Secretion.

The prostatic fluid from the rat is thin; it varies in appearance, sometimes being almost clear, but in most instances it is turbid; it has an alkaline reaction and a distinctive odor. When allowed to stand, a very fine granular material settles to the bottom.

If the prostate gland is taken out and the secretion obtained

from it after the coagulating gland has been removed, no special care having been taken to prevent contamination, it will be found that on mixing the prostatic secretion and the vesicle secretion a slight coagulation occurs; if, however, the coagulating gland is not touched and the prostate very carefully removed and the secretion obtained pure, no coagulation can be effected by it. I have tested this still further by adding large quantities of the prostatic secretion to the vesicle secretion and allowing the mixture to stand for a number of hours —8, 12, 24—there was not the slightest coagulation. I am convinced that the coagulating effect of the prostatic fluid as obtained by Camus and Gley and by Leuckart was due to contamination by the secretion of the adjacent coagulating gland.

Precipitation Reactions.—On heating, the prostatic fluid shows a large amount of protein material. With a half-saturated solution of ammonium sulphate, there is no change; with a saturated solution, there is a light flocculent precipitate. With a half- or a full-saturated solution of magnesium sulphate, there is no change. With dilute acetic acid, a slight precipitate is formed, which dissolves in excess. With alcohol, there is a heavy precipitate, which dissolves in dilute acid. The secretion dissolved in distilled water gives a very decided reaction for chlorides.

The Relationship between the Accessory Sexual Glands of the Rat and Guinea-pig.

The coagulating gland secretion of the guinea-pig was mixed with the vesicle secretion of the rat and an immediate and complete coagulation occurred.

The coagulating gland secretion of the rat was mixed with the seminal vesicle secretion of the guinea-pig; the coagulation was slow, not being complete under about eight hours.

A mixture of the seminal vesicle secretion of the guinea-pig in salt solution was made with that of the rat in salt solution; there was a decided precipitate, which dissolved somewhat on standing, and after about four hours had nearly disappeared. To this mixture the coagulating gland secretion of the rat was added; coagulation occurred promptly.

Further Considerations on the Nature of the Seminal Vesicle Secretion.

The question as to whether the vesicle secretion of the rat consists of only one substance, or whether it is a mixture, I am not at present able to answer. Reasoning from analogy it is certainly very probable that it is a mixture, but the following indications favor the view that it is largely composed of one substance:

If a large enough quantity of salt solution is used, all the material goes into solution. If this solution is slightly acidulated and boiled, there is no coagulation. This test of itself shows that the higher proteins are not present. When precipitated by nitric acid in the cold, and then heated, the precipitate redissolves and the solution becomes clear; this excludes some other proteins. And lastly, ammonia seems to give a quantitative precipitate; about this, however, I am not sure. As previously stated, I have tried by precipitation methods to settle the question, but I have not been able to do so satisfactorily. The above, then, are not cited to prove definitely anything, but are simply given as indications.

Histone Content.—At the outset I stated that the seminal vesicle secretion probably contains histone. My reasons for this view are as follows:

(1) The solution is only slightly clouded by heat. This reaction at once indicates that a number of other proteins are not present.

(2) It is precipitated by ammonia. None of the serum albumins, globulins, or albumoses is precipitated by this reagent.

(3) It is precipitated in a neutral medium by the alkaloidal reagents.

(4) Its reaction with nitric acid.

(5) It precipitates other proteins.

(6) It contains a relatively high nitrogen content.

I feel that the above reactions, all of which I have obtained in the vesicle material from the rat are certainly sufficient to indicate the presence of histone. It remains, however, to differentiate the histone from the substances just below it—the protamines.

The protamines also are not coagulated by heat. They also precipitate other proteins. They differ, however, in being thrown down by the alkaloidal reagents in an alkaline, but not in a neutral medium. They are not precipitated by ammonia. They have a much higher nitrogen content, and they do not contain sulphur. The first three characteristics are found in the vesicle secretion, but the last three are absent. It appears probable, therefore, that we are not dealing with a protamine.

It remains now to discuss the secretion from the seminal vesicles of the guinea-pig. This is extremely interesting from the fact that it has a number of properties of the histone and a number of those of the higher proteins.

(1) It corresponds in general physical and coagulation characteristics to that of the rat; it is soluble in the same fluid; it is not affected by heat; it is coagulated by the glandular secretion of the rat; it has a high nitrogen content; it has the same color protein reactions as that of the rat. All of these characteristics lend proof to the assumption that it has a similar content and probably contains histone, but on the other hand a number of striking characteristics of histone are absent, viz.: it is not precipitated by ammonia nor by alkaloidal reagents in neutral media; it does not coagulate other albumins and does not have the usual reactions with nitric acid. The absence of all of these tends to place it among the higher groups. In order to elucidate this point more fully it will be necessary to determine the hydrolytic products. This work I shall soon take up.

Does the Coagulating Gland Secretion Contain a Ferment?

The question of interest is whether this secretion acts by virtue of a contained ferment, or whether the reaction represents only a chemical or physical chemical phenomenon. At first I thought that I had to deal with a simple precipitation. Continued experimentation, however, has led me to believe

that the change is caused by a ferment: (1) Because there is such a very great disproportion between the two fluids, 1 to about 21,000; (2) When a minute quantity is added, no change is seen for several hours, and it is only after the lapse of from 18 to 30 hours that coagulation occurs; (3) The amount of ultimate coagulation is apparently the same for a fairly large quantity or for only a trace.

The Effect of the Various Secretions on the Motility of the Spermatozoa.

A very curious phenomenon was seen when I attempted to mix the seminal vesicle secretion solution with the material pressed from the vas of the rat. The spermatozoa became immediately clumped and it was found impossible to produce any homogeneous mixture. On microscopic examination the organisms were seen to be thrown in masses; they appeared as if they had been caught by something and for the most part they were without any motion. At the margins of the clumps a few were moving slightly, but they were held fast. What is still more curious, is that when the spermatozoa of the guinea-pig are mixed with the seminal vesicle secretion of the rat, a perfectly homogeneous mixture occurs and the organisms are actively motile. When the spermatozoa of the rat are mixed with the seminal vesicle secretion of the guinea-pig there is produced a uniform mixture and the organisms move actively. This is a very interesting observation and the cause for it should be more thoroughly studied.

The spermatozoa of the rat with its own coagulating gland secretion are motile and remain so for 2¾ hours.

The spermatozoa of the rat in its own prostate gland secretion are beautifully motile, and I have observed the continuance of this motility for eight hours.

The spermatozoa of the guinea-pig are actively motile in the coagulating gland secretion of the guinea-pig.

The spermatozoa of the guinea-pig are actively motile in its own prostatic secretion.

Summary.

1. The secretion of the prostate gland proper and that of a glandular structure adjacent to the seminal vesicles are radically different in physical and chemical characteristics.

2. In neither the rat nor guinea-pig does the secretion of the prostate gland coagulate the secretion of the seminal vesicles.

3. In both the rat and guinea-pig the secretion of the glandular structure adjacent to the seminal vesicles, which I have designated as the "coagulating gland," coagulates the secretion of the seminal vesicles.

4. This coagulation is produced by a very minute quantity of the secretion; one part of the secretion to about 21,000 parts of the seminal vesicle secretion is sufficient to produce the reaction. The phenomenon seems to be entirely different from blood coagulation.

5. The active principle in the secretion of the coagulating gland presumably belongs to the class of ferments.

6. The seminal vesicle secretion of the rat probably contains histone.

7. In the seminal vesicle secretion of the guinea-pig there is a substance which corresponds in part to histone and in part to the higher proteins.

8. The spermatozoa of the rat are immediately clumped when mixed with the seminal vesicle secretion of the same animal. This phenomenon does not occur in the guinea-pig, neither does the seminal vesicle secretion of the rat injure the spermatozoa of the guinea-pig; on the contrary they move actively in it.

It gives me pleasure to thank Drs. Howell and Abel for suggestions made in the course of this work, and also to express my appreciation to Dr. George Menge of the Government Hygienic Laboratory.

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PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS MEDICAL SOCIETY.

February 7, 1910.

Dr. Louis Hamman in the chair.

I. Heart Block: Report of Two Cases of Adams Stokes Disease. Dr. W. S. Thayer and Dr. F. W. Peabody.

Dr. Thayer reported two cases of Adams Stokes Disease (Heart Block) in patients whom he had under observation.

The first case was that of a white man, aged 53 years, of excellent family and personal history. Following a morning of violent exercise the patient had an attack of dizziness, and later was taken with general convulsive seizures. When seen by a physician, his pulse was markedly slow, 6-8 beats per minute, and very irregular; breathing was labored. The patient rapidly recovered from this attack and felt perfectly well. One week later, however, a second attack occurred, and when seen by Dr. Thayer the patient was quite pale, breathing very irregular and almost pulseless. After a few convulsive seizures there was a general flushing of the skin, and the radial pulse returned. The patient was brought to the hospital and cardiographic records made by Dr. Peabody clearly showed a marked disproportion in the rates of contraction of the auricles

and ventricles. The auricular rate was 120 per minute, and the ventricular 30 per minute. The patient made a complete recovery.

The second case was that of a colored man, over eighty years of age, who for some time previous to his admission into the hospital complained of "spells of shortness of breath." For long periods of time, the heart was regular in rhythm, but at times numerous "dropped beats" were to be noted at the wrist. This condition could be brought on by applying digital pressure over the vagus nerve in the neck, when the ventricular pulsations could be affected, and the pulse rate decreased and made markedly irregular. Carefully made cardiograms showed a slight lengthening of the auricular intervals without any apparent delay in the conduction time. This patient left the hospital and has since been lost track of.

II. An Experimental and Clinical Study of the Functional Efficiency of the Kidney by Means of Phenolsulphonaphthalein. Dr. L. G. Rowntree and Dr. J. T. Geraghty.

The first part of Dr. Rowntree's paper dealt with the history of the various attempts made to estimate the functional efficiency of the kidney by means of substances taken by mouth or subcutaneously. The time of the appearance of these substances in the urine was taken as a rough estimate of the ability of the kidney to excrete them. Among the substances proposed are methylene blue, indigo carmine, rosanine and phloridizin. Unfortunately the results of the use of these drugs are most disappointing, and few conclusions can be drawn from them. The essentials for a satisfactory drug for this test, is that it shall be one that is practically all excreted by the kidney, that it shall have no toxic effect and that the time of excretion be as short as possible.

In the use of a new phenolphthalein derivative, phenolsulphonaphthalein, it is believed that all these essentials are present.

Only a small amount of this drug is necessary and it apparently undergoes no chemical change in the body, as from sixty to eighty-five per cent is recovered in from two to four hours after its administration. The detection of the drug in the urine is quite easy, the addition of a few drops of alkali to the urine in the presence of the drug will give a definite color reaction. Phenolsulphonaphthalein differs from all other phthaleins in that none of the drug is secreted by the bowel, practically all being excreted by the kidney.

Dr. Geraghty reviewed the results of the use of this new drug in a large number of cases of suspected renal functional insufficiency and the results are most gratifying. Further report will be made at the completion of their experiments.

February 21, 1910.

Meeting of the Johns Hopkins Medical Society. Dr. Louis Hamman in the chair.

I. Recent Advances in our Knowledge of the Causation of Tropical Diseases. Dr. J. L. Todd, McGill University, Montreal, Canada.

In a masterly review of the voluminous literature on tropical diseases, Dr. Todd outlined the most conspicuous advances in the study of these diseases. He said that the English and French governments in their efforts at colonization of the tropics have found that the conquest of these countries depends upon the conquest of the tropical diseases. Institutional work, including both laboratory and field study along these lines, with the support of the home government, is imperative.

The immense bibliography of the "sleeping sickness" disease, permits of the ascertaining of the weak points by which the disease can be combated. In the study of this disease, attention has been directed along three channels; first, as to the habits of the *glossina palpalis* or tsetse fly, through whose bite, the disease is given to man; second, as to the treatment of the disease itself; third, as to methods of early diagnosis of the disease. Among the most interesting facts regarding the tsetse fly, he says that the fly may still be able to transmit the disease seventy-five days after having bitten an infected individual. That the ordinary trypanosomes may undergo changes in the fly resembling those changes which occur when the rat serves as a host for the parasite.

Both arsenic and antimony have trypanosomicidal properties, and these two drugs are more effective when given together.

A curious fact observed by the natives is that whenever any of their number presents an enlargement of the cervical glands, that individual is most likely to be infected with the trypanosomes. Examination at autopsy has proven the truth of this belief, both for animals and for man.

Dr. Todd's paper was well illustrated by means of microscopic preparations, charts and living hosts of the trypanosomes.

Discussion.

Prof. J. J. Abel.—While Dr. Todd has given you a most interesting outline of the recent investigations in tropical diseases, he has modestly failed to mention his own connection with the many advances made in combating these diseases.

At great personal risk both Dutton and Todd have accomplished many important pieces of work both in the field and in the laboratory. They have laid great stress on the gland palpation and even gland puncture in the diagnosis of this disease. My own particular interest in the subject has been entirely in the therapeutic side, and for some time I have been experimenting with various synthesized products of arsenic and antimony as to their trypanosomicidal properties.

While it is true that by means of these two drugs the blood of small animals, such as the rat, can be cleared of the trypanosomes, the same does not seem to hold true for larger animals. The question of the size of the dose is an exceedingly difficult one to ascertain.

II. Clinical Observations upon Intestinal Putrefaction; with Remarks upon Harmful Effects of Purgatives. Dr. D. L. Edsall, University of Pennsylvania.

Dr. Edsall insists that it is the duty of the practitioner as well as the consultant, not only to examine the rectum, but to examine the fæces. He believes that in a great number of

cases showing "neurasthenic symptoms," that these symptoms may be due to chronic intestinal putrefaction. Two types of changes may be recognized; the fermentative, due to the ingestion of an excess of carbohydrates, in which the symptoms are myasthenic in nature, and the putrefactive, due to an excess of proteids, in which headaches are the main cause for complaint. The latter cases, showing putrefactive changes, seem to be much easier to handle.

In the routine examination of the fæces Dr. Edsall does not resort to the use of a test meal, but prefers to draw conclusions from the study of the stool after the patient has ingested his normal or accustomed meal.

Attention must be paid to the fat and carbohydrate disturbance and the fæces should be allowed to stand for varying periods of time, at room temperature to determine the rapidity of fermentative and putrefactive changes.

Following the habitual use of purgatives, there is evidence of marked irritation of the gastro-intestinal tract, and Dr. Edsall believes that many of the purgatives themselves may cause the very symptoms for which they are given. The field for the use of mild purgatives has become an extremely limited one.

Discussion.

Dr. J. H. M. Knox.—Dr. Knox discussed the occurrence of intestinal, putrefactive and fermentative changes in children. The control of a healthy intestinal condition in children necessarily depends upon the choice of a suitable diet. He cited several cases of successful "lactic acid therapy" in children showing marked restlessness and sleeplessness. Here the intestinal flora was changed through the administration of the Bulgarian strain of the lactic acid bacillus.

February 28, 1910.

Meeting of The Laennec Society for the Study of Tuberculosis. Dr. Henry Barton Jacobs in the chair.

I. Exhibition of Cases: (a) Pneumothorax. (b) Multiple Progressive Serositis. Dr. Louis Hamman.

The first case exhibited was that of a young white man, aged 20 years, who came to the Phipps Dispensary on November 2, 1909, complaining of discomfort in the right side of his chest. Examination at that time was negative except for a slight prominence of the right clavicle and a diminished movement of the right side of the chest and a few scattered crackles on deep inspiration. Two weeks later, November 15, the patient was seized with a sharp pain in the right side of the chest and a sense of suffocation.

Examination revealed no movement of the diaphragm on the right side and an almost total absence of the breath sounds. A diagnosis of pneumothorax was made. A radiograph of the chest taken at that time confirmed this diagnosis. The patient was kept under observation and at the end of the first week little change was noted in the physical signs; two weeks later slight movement of the diaphragm could be detected on the left side.

At the end of the third week, the lung on the affected side began to expand. The striking features of this case were the comparative mildness of the symptoms and the slightness of the physical signs. It is difficult to offer an explanation of the etiology of this condition. The rupture of small emphysematous blebs on the surface of the lung permit air to gain entrance into the pleural sac, and formation of a pneumothorax. The healing of the bleb and reabsorption of the air permits the lung to expand.

It is interesting that this case failed to react to repeated tuberculin test.

The second case was that of a white man, aged 25 years, who for several months complained of "fever and chills." During his stay in one of the city hospitals he was treated for malaria and typhoid fever. On admission to the hospital he developed a well marked hydrothorax, which persisted and necessitated tapping ten to twelve times.

On examination, he showed a most remarkable cyanosis of the face, neck and upper portion of the chest; with engorgement of the superficial veins. An extremely coarse pleural friction rub was noted over the left front of the chest, but there were no signs of intra-pulmonary trouble. The heart sounds were feeble; there was no marked enlargement on percussion, although the radiograph showed slight enlargement of the right side of the heart.

The abdomen was distended; there was slight movable dulness, and a huge liver, which produced a prominence both in the mid line and in the right upper quadrant; the spleen could just be palpated. The case was regarded as one of multiple progressive serositis. This patient gave a marked reaction to tuberculin and before the period of injections for treatment showed at times a marked sub-normal temperature reaching as low as 94° on several occasions.

Dr. G. H. Whipple exhibited a number of pathological specimens illustrating the different phases of serositis and including a typical "iced liver" with its thick glistening capsule.

II. The Value of X-rays Examination in the Diagnosis of Pulmonary Diseases. Dr. Charles L. Minor.

In a most interesting paper Dr. Minor outlined the use of the x-ray examination as an aid to the diagnosis of pulmonary diseases. He emphasized the great importance of a thorough auscultation and percussion of the chest before fluoroscopy. His x-ray findings are only confirmatory in character and corroborate the physical signs. In a few cases, deep seated foci are revealed by the x-ray and early enlargements of the mediastinal glands are made out which would escape detection in any other way. As claimed by Williams, the slightest limitation of movement of the lungs is often made out and antedating any possible change in the physical signs. He finds fluoroscopy of great service in the detection of early apical lesions only when they are accompanied by physical signs, enlarged glands, thickened pleura and intra-lobar empyema.

March 7, 1910.

Meeting of Johns Hopkins Medical Society. Dr. Louis Hamman presiding.

I. Anaphylaxis and its Relation to Clinical Medicine. Dr. John F. Anderson, Washington, D. C.

The earliest experimental work upon the subject was that by Richet, working with actinia poison in dogs. Richet coined the word "anaphylaxis" from two Greek words ανα against, and φυλάς guard, or φυλαξις protection. He considered the condition an opposite one to that of prophylaxis; but we now know that the phenomenon, instead of being a disadvantage is probably an important step in the protection of the organism against a certain large class of infections.

The condition of anaphylaxis may be transmitted from the mother or may be acquired, and it may be brought about by the introduction of any strange proteid into the body. A well known clinical instance of anaphylaxis is that induced in an individual by a second vaccination. In the reaction to a primary vaccination the incubation period is about four days; i. e., in about four days the local symptoms at the point of vaccination appear or become distinctive and there is more or less constitutional disturbance. In a secondary vaccination, or a vaccination following a successful vaccination after some months, the period of incubation is much shortened and the clinical reaction very much lessened. In other words, the power to react has been so changed that, instead of an incubation period of four days, we have an incubation period of 24 to 36 hours. This acquired power of immediate response is an evidence that protective bodies have been formed within the organism; but there is no absolute immunity in this class of infections, though, on account of the power of immediate reaction the individual is protected.

Other well known clinical instances of anaphylaxis are the tuberculin and mallein reactions in tuberculosis and glanders. Neither of these bacterial products is harmful in moderate amounts to a healthy individual, but a person suffering from tuberculosis or glanders will respond to a very small amount of tuberculin or mallein respectively.

It has been known since the sixteenth century that the whole blood of certain animals is poisonous when transfused or injected into man. Many workers have found that the blood serum of an animal of one series is frequently poisonous when injected into an animal of another species, but that the serum of the horse, and the donkey to a large extent, lacks such poisonous properties. Large amounts of horse serum may be injected into man, the rabbit, the guinea-pig and other animals without causing very unpleasant results except possibly a slight reaction at the site of inoculation. In a certain proportion of cases, however, the injection of horse serum into man is followed by the syndrome described and named by von Pirquet as the "serum disease." In a very small percentage of cases the injection of horse serum into man has been followed by sudden death.

Horse serum, when injected into guinea-pigs, is a comparatively bland and innocuous substance, but these animals may be rendered so sensitive that a second injection of horse serum may produce death or at least very severe symptoms.

The first injection of the foreign protein has so changed the mechanism of the animal's organism as to render it very susceptible to the second injection. A certain time must elapse between the first and the second injection in order that this hypersusceptibility may be manifested. This time varies from 5 to 12 days and is in close accord with the period of incubation of the "serum disease" which von Pirquet places at 8 to 13 days.

As the first experimental work with anaphylaxis was done with horse serum, it was thought that diphtheria antitoxin had some part in this toxic action of the serum; but as it was soon found that the phenomenon could be induced by any protein such as those which have just been named, it was seen that diphtheria antitoxin had absolutely no part in the production of the phenomenon.

The toxic action following the injection of the serum is due to a protein in the horse serum and is entirely independent of the antitoxic properties of the serum. It would be exceedingly unfortunate if the studies upon anaphylaxis should in any way prevent the usage of diphtheria antitoxin or any other therapeutic serum when it is indicated.

The symptoms produced by the injection of horse serum into a susceptible guinea-pig are exceedingly characteristic. They are apparently the same where the animal be given the injection subcutaneously, intravenously, intraperitoneally or into the brain. When injected into the brain the symptoms appear very much more quickly and frequently with explosive violence in some instances the animals dying within three minutes after the injection.

At least a certain time must elapse between the first and the second injection of the protein before the anaphylaxis is manifest. This time or period of incubation is from 7 to 12 days, which is about the same as for the serum disease in man and is very similar to the period of incubation of a number of the infectious diseases. The optimum period or interval for the development of anaphylaxis is after three weeks.

Rosenau and Anderson believe that the portion of the protein which sentitizes the guinea-pig is the same as that which later poisons it and Wells has brought forward experimental data to show the two are at least in the same protein molecule or are two separate portions of the same molecule. The effect of heat in modifying or destroying the anaphylactic properties of proteins depends upon its effects in rendering the proteins insoluble rather than the production of chemical changes in the proteins.

Various procedures, such as the administration of atropine, injections of chloralhydrate plus urethane and adrenalin, pure oxygen and production of ether or alcohol, narcosis, all seem to exert favorable influence upon the outcome of anaphylaxis when given a short time previous to the intoxicating injection.

An interesting fact in connection with the specificity of the reaction, is that guinea-pigs may be sensitized with three proteins at the same time, and that the animal differentiates the anaphylactic-producing substances in a separate and distinct

manner and is found to be susceptible to a second injection of each one of the three substances in the same way that an animal is susceptible to three separate infectious diseases. Guinea-pigs may readily be sensitized by feeding them a protein for several days and when tested for their susceptibility after 14 days by an injection of the protein they are found to be sensitive.

The experiments upon the transmission of anaphylaxis by the female to her young are of very great interest in relation to the question of an inherited tendency to tuberculosis in children born of a tuberculous mother. It is generally accepted, Dr. Anderson believes, that the children of a tuberculous mother, instead of having an immunity to tuberculosis, on the other hand, are more susceptible. Only very rarely is the child born with the seeds of the disease in its system, but that there is transmitted from the mother to her offspring a tendency to the disease.

Man may be sensitized in the same way as has been shown to be in the case with guinea-pigs and von Pirquet and Shick in their work upon the serum disease found that when the second injection was given, after an interval of 14 days to four months, they obtained what they termed their "immediate" reaction in which the symptoms of the serum disease appeared at once or within 24 hours; but that when the interval was more than four months they obtained little or no immediate reaction, but what they termed the "accelerated" reaction, in which the symptoms of the serum disease appeared on 5th to 8th days.

The unfortunate accidents, such as collapse and sudden death, following serum injections depends more upon individual sensitization than upon the so-called toxicity of the serum used. It has been found that serum which has not produced untoward symptoms when injected into man is fully as toxic for sensitive guinea-pigs as serum, the use of which has been followed by serious symptoms or even sudden death when injected into man. It is a most interesting fact, that many of the cases of sudden death following the first injection of serum in man have been in asthmatics or in persons who have an idiosyncracy to horses. That is, there are certain individuals who show peculiar symptoms resembling hay fever or asthma, when in the vicinity of horses or horse stables and these individuals are the ones so extremely susceptible to the first injection of serum. The knowledge of the fact that the injection of horse serum into such persons is a danger must certainly be taken into consideration in the use of antitoxin.

Discussion.

Dr. C. F. v. Pirquet.—Dr. Anderson did not tell you that his work with Dr. Rosenau was one of the most complete and valuable contributions to the subject. They were the first to establish a quite definite test as the basis of their investigations: the immediate death of a guinea pig at the second injection of horse serum and other substances. And with this test, they investigated in numerous and painstaking experiments one question after the other. Everything Rosenau and Anderson have established stands firm. Anderson's special work was about the transmission of anaphylaxis to the offspring. His experiments are quite clear, but as to the conclusions which he mentioned in regard to tuberculosis, I am not fully of his opinion. If an inherited tendency to tuberculosis is due to a transmission of anaphylaxis, we ought to find a positive tuberculin reaction in children of tuberculous mothers. This is not the case. Children of tuberculous mothers or calves of tuberculous cows give negative tests, except if they have acquired an active tuberculous lesion by infection. I do not believe in an inherited tendency: the frequency of tuberculosis among children of tuberculous parents is due to the great probability of infection in early age, if one of the parents suffers from an open tuberculosis.

II. Acute Pancreatitis and Urinary Findings. Dr. G. H. Whipple.

The report consists of two parts: the first dealing with the Cammidge reaction; the second with the presence of lipase in the urine. The experiments were performed by four men—Mr. Chaffee, Mr. Fisher, Dr. King and Dr. Whipple, and by various repetitions and controls the personal equation was eliminated.

Acute pancreatitis was produced in dogs by the injection of 4 or 5 cc. of pig's bile into the large pancreatic duct. Visible ecchymoses appeared within five minutes after this injection and together with the bile-stained edema, indicated the extent and severity of the lesion which developed very rapidly. The Cammidge test "C" was used in all the experiments. Both catheterized and filtered cage urine uncontaminated with feces were used and no difference noted in these types. All the animals with acute, hemorrhagic pancreatitis gave a positive Cammidge test with one exception; the crystals obtained corresponded in morphology and solubility to those described by Cammidge.

Animals poisoned with chloroform as a rule gave a positive Cammidge reaction. Such animals were suffering from extensive necrosis of the liver, and it was thought that the necrosis of the liver cells was responsible for the positive test.

Two animals suffering from bronchopneumonia gave a positive Cammidge test. A piece of pneumonic dog's lung was hydrolized with five per cent sulphuric acid for two hours, neutralized with barium hydroxide, and the clear filtrate injected into the peritoneum of dog whose urine previously gave a negative Cammidge reaction. This animal's urine after the injection gave a very beautiful Cammidge test; and the test persisted in the animal's urine for one week. At the end of this time operation showed a normal peritoneal cavity, pancreatic, liver, spleen, and kidney tissue.

A second experiment using 250 g. of a human pneumonic lung (gray hepatization) was performed, (hydrolysis for six hours with five per cent sulphuric acid, neutralization with barium hydrate and concentration of the clear liquid to 500 cc.). Fifteen cc. of this concentrated extract injected intraperitoneally gave a positive Cammidge reaction in the urine of an animal which previously was free from the reaction. The Cammidge test applied to the fluid itself gave a positive reaction. Routine examination of dogs in the laboratory showed a positive reaction in a few perfectly normal female dogs, in one dog shortly after pregnancy and in other dogs recovering from extensive operations not involving the pancreas.

The Cammidge test was applied to several patients who afterwards came to post-mortem examination. One case suffering from an abscess of the pancreas gave a positive reaction. A second case of acute leukemia gave a positive test; but the pancreas at post-mortem was found to be normal. A few cases of clinical chronic pancreatitis gave a positive test. These results could not be controlled by post-mortem examinations.

It is evident from our experiments that the Cammidge test is not specific for acute or chronic changes of the pancreas. The disintegration of any cells in the body may give the reaction or even artificial hydrolysis of any animal tissue may give substances which will appear in the urine and give the characteristic crystals. It is possible that the disintegration of the polymorphonuclear leucocytes is an important factor in the production of this unknown substance. Determination of the melting point of purified crystals does not correspond with the reports given by Cammidge. The melting point was found at about 140° C.

PART II.

The presence of Lipase in the Urine.—Catheterized urine was used in all experiments, and the same series of animals was studied for this reaction. The technique of the test has been recently described by Drs. Winternitz and Meloy. The reaction depends on the ability of the ferment lipase to split ethyl-butyrate with the setting free of butyrate acid which is estimated by titration with 1/20 normal sodium hydroxide. Litmus is used as an indicator.

In animals suffering from acute hemorrhagic pancreatitis, this ferment is constantly present in the urine, most marked for the first three days, but present usually for a week. After anesthesia (ether or chloroform), this ferment appears in the urine after a few minutes of anesthesia and persists some hours after the anesthesia. It is present in a considerable amount. This is not due to a rise of the serum lipase which remains practically constant, and must be due to the increased permeability of the renal epithelium allowing the escape of this ferment.

Ligation of the body of the pancreas causes the appearance of a small amount of the ferment in the urine, and the condition persists for one to two weeks. The ferment does not appear in the urine in cases of acute peritonitis; for example, due to the rupture of a distended gall bladder. Animals with jaundice or pneumonia do not give the reaction. Many normal dogs have been examined, and the reaction was negative in all but one. This animal was in the late weeks of pregnancy, and this may explain the finding.

A few human cases have been examined, and the reaction was negative in all except one diagnosed as probably a large abscess in the region of the pancreas. The ferment was present in the urine in very small amounts only for three days following the operation and drainage of this abscess cavity. It is believed that the examination of the urine for this ferment may be of value in cases of acute hemorrhagic pancreatitis, particularly at onset.

March 11, 1910.

Special Meeting.—The Johns Hopkins Hospital Medical Society in conjunction with the Neurological Section of the Medical and Chirurgical Faculty. Dr. Louis Hamman in the chair.

I. Studies in the Comparative Development of the Nervous System. DR. STEWART PATON, Princeton, N. J.

In a most interesting talk Dr. Paton reviewed his recent observations made in the study of the egg of the scyllium canicula, a species of Mediterranean shark. By means of a small fenestra made in the capsule of the egg the growth of the embryo could be made while the egg was kept in the natural environment.

The first movements observed consisted in a slight motion of the head and tail of the embryo, which began when the embryo reached the length of 4 mm. Three days later a slow peristaltic motion of the heart was noted. The movements of the heart are affected by the temperature of the water and also by the addition of sodium chloride up to one and three per cent solutions. The addition of urea to the water has a marked stimulating effect for the adult heart but not for the embryo heart.

Up to the stage where the embryo reaches the length of 5 mm. no nervous system is present from an anatomical standpoint. Still certain reactions are present which may fall into the class observed in the medusa. Cocaine in very large doses has no effect upon the movements of the embryo below the 7 mm. stage, but above this stage the drug exercises its characteristic effects.

Between the 9 and 14 mm. stage, when the heart is excised, very little effect is noted upon the swimming movements of the embryo. The sympathetic nervous system is supposed to be differentiated at the 14 mm. stage. According to Loeb the nervous system acts simply as a regulator and absolutely no specific quality can be ascribed to it. The guiding effect of the nervous system comes on at the 14 mm. stage and at that time autonomy asserts itself. As early as the 4 mm. stage, at a time when there is no evidence of any cardiac activity, an unbroken tract of protoplasmic cells can be made out extending from the myotome to the spinal column and from the spinal column to the (ectoderm) periphery. These tracts seem able to conduct impulses at this stage, still it is impossible to pick out just which cells are destined to become nerve cells. It is thought that these complicated nervous tracts exist in a physiological sense long before any anatomical destruction of nervous tissue can be made out. It is not until the embryo reaches the 6 mm. stage that the vagus nerve reaches the heart; up to this time the heart has been beating uninfluenced by the nerve.

II. The So-called Thyroid Carcinoma of the Brook Trout and its Relation to Ordinary Goitre. DR. DAVID MARINE, Western Reserve University.

Opportunity was offered to Dr. Marine to study the occurrence of thyroid enlargement in brook trout and other species of fish in the Michigan State Fish Hatcheries. In the ponds

and tanks of these hatcheries, a large number of fish were found to be affected with hyperplasia of the thyroid; often more than half the number of fish were found thus affected in several of the ponds.

Certain associated changes were noted in these goitrous fish. The fish were noted to be large for their age, excessively fat and as a rule showed excess of skin pigment. Pigment was also found present in the thyroid and internal organs. Constant enlargement of the spleen and lymphoid tissue was observed just as is so often seen in mammalian goitre. Careful study was made of the habitat of the fishes, the flora of the ponds, the effects of increase and decrease of the water supply: and the nature of the food furnished was also thoroughly investigated.

Inoculation experiments were tried but all gave negative results. The question of therapy was taken up and various strengths of iodine solution were supplied to the affected fish and marked changes were soon to be noted. Iodine was found to have a specific action on the hyperplasia of the thyroid tissue; i. e., the hyperplasia ceased and the gland showed colloid accumulation, the blood supply to the gland was reduced and the blood vessels underwent a type of obliterative endarteritis.

The following will serve as a summary of Dr. Marine's views concerning the carcinomatous nature of this hyperplasia. Is this thyroid hyperplasia true carcinoma? In view of the facts that young fish are more affected than old fish: that iodine stops the hyperplasia and causes it to return to the colloid state; that removal of the fish from the ponds to the open brook also effects a cure; that the clinical incidence of tumors is directly related to the water supply; that the severity of the disease as determined by histological examination is likewise directly related to the water supply, we cannot accept the prevailing opinion that the disease is true cancer. On the other hand we believe that the disease as studied by us is an extreme illustration of endemic goitre, the end stage of which is cretinism. The opinion that it is cancer is based purely on anatomical studies—the essential fact being that the growing thyroid invades bone, muscle, etc. Such findings in mammalian tissues are strong evidence of malignancy but this standard cannot be applied to fish thyroids for the reason that any growth of a widely and loosely distributed nonencapsulated gland would give the histological appearance of invasion of the surrounding tissues.

Discussion.

Dr. H. R. Gaylord.—This disease is found in the stock waters of New York, the disease is quite common, and factors enter into its occurrence which do not belong to the conditions found in fish hatcheries alone.

Young fish are undoubtedly much more susceptible to the disease than the older fish. I do not believe that spontaneous recovery is any evidence that the growth is not of a malignant nature, nor do I think, at the present time, a therapeutic test such as suggested by Dr. Marine will supplant the microscopic test. The standard of encapsulation is not entirely satisfactory and in our observations in cancer in rats we often find that rapidly growing soft carcinomatous growths change over into a less malignant form and show marked adenomatous changes.

NOTES ON NEW BOOKS.

An English Handbook to the Paris Medical School. (With Map.) By A. A. Warden, M. D. Second edition. Price, 50 cents. (*Philadelphia: P. Blakiston's Son & Co., 1910.*)

This small paper-bound volume contains chapters on post-graduate work in Paris, the faculty of medicine, the hospitals, and other subjects of interest to the prospective student in the city. It is neatly and compactly arranged, and most serviceable for those thinking of going to Paris to study.

A Text-book of Physiology: for Medical Students and Physicians. By William H. Howell, Ph. D., M. D., LL. D., Professor of Physiology, Johns Hopkins University, Baltimore. Third edition. Thoroughly revised. Price, $4.00. (*Philadelphia and London: W. B. Saunders Company, 1909.*)

A detailed review of this text is uncalled for. We may observe with satisfaction that the revision of the book has fully justified the short interval which has elapsed since the last edition appeared. The problem of altering the presentation so as to include the more recent advances in physiology without a corresponding increase in the number of pages is no simple one, and the author is to be congratulated upon the success with which this has been done. Among the more recent contributions incorporated in this edition may be mentioned the application of Einthoven's string-galvanometer to physiological problems; the investigation of physiological processes whether they be chemical or physical according to their temperature coefficients after van't Hoff's law; the newer work on the coagulation of the blood; the physiological importance of the venous blood pressure and Rubner's work on nutrition and growth.

A Text-book on the Practice of Gynecology. By William Easterly Ashton, M. D., LL. D., etc. Fourth edition, revised and enlarged. Price, $6.50 net. (*Philadelphia and London: W. B. Saunders Company, 1909.*)

This new edition of Dr. Ashton's well-known work presents numerous alterations and revisions. The general plan of the book has not been changed, however, and it is pleasing to note that the same wealth of detail, clearness, logical arrangement of subject-matter and comprehensiveness which have made previous editions so acceptable both to practitioners and students are conspicuously in evidence in this one. The author happily assumes throughout an entire ignorance on the part of the reader of the subject-matter under discussion; and if, on this account, many paragraphs seem elementary in character and superfluous to the experienced specialist, this objection is fully offset by the judicious use of bold type, which renders selective reading quite easy, and by the further important consideration that an authoritative opinion on detail is made accessible to the beginner.

Medical gynecology is very fully and satisfactorily considered, a feature of the book that should prove very attractive to many practitioners.

The chapters on certain diseases of the urinary system, on

ectopic gestation, on shock, and on peritonitis are among the more important ones that have been fully revised in accordance with recent advances.

The illustrations are numerous and, while not of high artistic merit, yet are, for the most part, clear and accurate, and constitute an important adjunct to the text.

The book can be safely recommended as an authoritative work on gynecology that justly deserves the widespread recognition already accorded it.

E. H. R.

A Text-book of the Practice of Medicine. By JAMES M. ANDERS, M. D., etc. Ninth revised edition. Illustrated. Price, $5.50. (*Philadelphia and London: W. B. Saunders Company, 1909.*)

The appearance of a ninth edition of Anders' Practice is evidence that there is a demand for the book. In reviews of former editions we have commented on the lack of originality of method and aptness of presentation in this work, a fault shared by many other similar compilations. This new edition has been rewritten in parts, but maintains the same general character. The illustrations are rather disappointing, especially the color work.

The Elements of the Science of Nutrition. By GRAHAM LUSK, Ph. D., M. A., F. R. S. (Edin.), Professor of Physiology at Cornell Medical School, New York. Second Edition, revised. (*Philadelphia and London: W. B. Saunders Company, 1910.*) Price, $3.00.

"This, the second edition, differs chiefly from its predecessor in containing facts which have been brought to light during the past three years." In the March, 1908, number of this journal this work was warmly reviewed, and it is merely necessary to call attention once again to this most excellent work. No better book of its size exists in English.

Esquisses cliniques de Physicothérapie, Traitement rationnel des Maladies chroniques. PAR LE DOCTEUR J. A. RIVIÈRE, etc. (PARIS: *Imprimerie Brucky et Cie., 1910.*) Price, f.7.50.

Dr. Rivière is a very ardent advocate of mechano, electro and hydrotherapy in all their forms, and there is no doubt that those who have carefully used these methods of treatment do secure results with them which others who use them but seldom rarely obtain. But it is doubtful whether the results are always so brilliant as the author would seem to claim, and whether the explanations of their physiological actions is based on more than pure hypothesis; and, finally, whether physicotherapy is of real value in as many different diseases as the author believes. The author's style is not as clear and simple as that of most French writers, and the book is not, therefore, easy reading, but deserves consideration because of the author's professional standing. Though his views may not always be sound, yet those with open minds, anxious to learn the value of physicotherapy will do well to look over this work.

The Medical Annual. A Year-Book of Treatment and Practitioners' Index, 1910. 28th year. (*Bristol (Eng.): J. Wright & Sons.*) Price, 8/6.

This English annual is one of the best published. It has a large staff of well-known English surgeons and physicians, two from Philadelphia, Ashhurst and Deever, and Novak, of Baltimore. The collaboration of these men furnishes the profession with a useful and well-illustrated manual, which contains more general information rather of use to English than foreign practitioners than any other work of this nature. The contents are so numerous that any abstract of them would give but a poor idea of the variety of subjects treated, but one paper deserves special attention, "Sea-Water Treatment," by S. Robert Simon, M. D., of Paris. The value of injections of sea water is certainly very remarkable if one may judge from the accompanying photographs of patients before and after treatment.

Department of Neurology, Harvard Medical School. Vol. IV. (*Boston, Mass., U. S. A., 1910.*)

This volume contains 12 neurological papers on widely different subjects, which have all appeared either in the Boston Medical and Surgical Journal, the Journal of Nervous and Mental Diseases, or elsewhere. The authors are Knapp, Taylor, Putnam, Waterman and Patch. Such collections are of value in all medical libraries, as they are more easily consulted than the various journals which are frequently missing.

The Sexual Life of Woman in its Physiological, Pathological and Hygienic Aspects. By E. HEINRICH KISCH, M. D., Professor of the German Medical Faculty of the University of Prague, etc. Only authorized translation into the English language from the German, by M. EDEN PAUL, M. D. Illustrated. 1910. (*New York: Rebman Company.*) Price, $5.

This work is divided into three parts: the Sexual Epoch of the Menarche, the Sexual Epoch of the Menacme and the Sexual Epoch of the Menopause. "By 'menarche' the author means the period of life when menstruation as a sign of puberty first makes its appearance, and by 'menacme,' the culmination of the sexual development of woman, during which the processes of reproduction, copulation, conception, pregnancy, parturition and lactation occur." Both French and German writers have devoted more attention to the sexual side of life in both sexes and its influence on moral and physical development than have Americans and Englishmen. To the latter the subject is often distasteful, and they have not as thorough a knowledge of its importance as they ought to have. This book is only one of very many dealing with the subject and will doubtless find interested readers, even in spite of its size. It is discursive rather than profound and is hardly as the author states "a contribution towards the solution of the sexual problem," at least the solution does not appear any nearer after reading the book. The writer has collected much material and writes with a serious purpose, though as in almost all these works there is at times an unpleasant note, but on the whole he has handled a difficult subject as well as most.

Male Diseases in General Practice. By ELDRED M. CORNER, M. C., B. Sc., F. R. C. S. (*London: Oxford University Press, 1910.*)

This moderate-sized book, of about four hundred and fifty pages, fulfills its mission, as announced in the title, quite well. Dealing entirely with diseases of the male it includes only the urethra and no more of the urinary apparatus. The chief criticism of the work should be directed against the brief manner in which the prostate and its conditions are dwelt upon, as well as the verum montanum, both of which deserve more attention if we are to judge by their frequent involvement in pathological processes and the sometimes obscure symptoms of which they are the cause. The chapter on the urethra is hardly as full or as broad as one would expect to find in a book devoted to male diseases, particularly in regard to treatment. The chapters on the external genitalia are full and very excellent. Altogether, with large type and an easy style, it is a pleasant book to read as well as one worth the while of even a very busy practioner.

M. L. B.

Proceedings of the Imperial Malaria Conference, Held at Simla, in October, 1909. (*Simla: Government Central Branch Press, 1910.*)

The importance of malaria as a health and life-destroying factor in the East is evidenced by the calling of this conference, and the publication of its proceedings. Malaria is now so well controlled

in this country that it is hard to believe in the enormous mortality still caused by it in certain parts of the world. By students of hygiene, and others interested in malarial questions and problems, this report will be read with care, for the work done by English government officers, both lay and medical, along broad hygienic and scientific lines is of such high quality, that their writings cannot be neglected if one desires to be well informed on the matter in hand.

New and Nonofficial Remedies, 1910: Containing descriptions of articles which have been accepted by the Council on Pharmacy and Chemistry of the American Medical Association, prior to Jan. 1, 1910. Price, paper, 25 cents; cloth, 50 cents. 256 pages.

This is the second year of the publication of this work, and practitioners and pharmacists should welcome it warmly, for it contains in compact form information difficult to find without long search. Many of the drugs described are much used, so that it is all important for a doctor, who desires to use them, to be able to find readily, as he here can, an accurate description of them. The names of the compilers, who are all highly trained scientific men, gives the work a stamp of thoroughness and value.

Handbook of Therapy. (*Chicago: American Medical Association, 1910.*) Price, $1.50.

This is a new venture on the part of the directors of the American Medical Association. For the use of the general practitioner and medical student there has been culled from the journal of the association the most important matter on therapeutics which has appeared in it in the past few years. Here are brought together the views of all classes of doctors at home and abroad on various drugs and treatments. Such a compilation has its advantages as well as its disadvantages, but the latter would seem to outnumber the former, and render the book of little real value to the medical student. For the general practitioner it may prove more serviceable, but the handbook cannot really prove of great service to any one, for it is not sufficiently authoritative. In therapy the experience of the best masters is wanted perhaps more than in any other branch of medicine, that harm may not be done the patient, and so it would be wiser when in trouble to turn to the leading works on therapeutics rather than to this small manual.

Progressive Medicine. Edited by Hobart Amory Hare, M. D., etc., assisted by H. R. M. Landis, M. D., etc. Vol. I. (*Philadelphia and New York: Lea & Febiger, 1910.*)

The contributors to this volume are Frazier, Ruhräh, Crandall, Kyle and Dent, and their respective chapters on Surgery of the Head, Neck and Thorax; Infectious Diseases, including Acute Rheumatism, Croupous Pneumonia and Influenza; The Diseases of Children; Rhinology and Laryngology; and Otology are all well prepared. Abstracts of the leading articles on these subjects are presented and references given to others, and each contributor adds something of value by expressing his own opinion upon the questions discussed.

The Propaganda for Reform in Proprietary Medicines. Sixth edition: Containing the various exposes of nostrums and quackery which have appeared in The Journal of the American Medical Association. Price, paper, 10 cents; cloth, 35 cents. 292 pages. Illustrated.

The value of this small book is shown by the fact that this is its sixth edition, and we hope that many more editions will be called for. The more it gets into the hands of the intelligent laity the better. Our people need to learn the uselessness and harm that may come to them from taking proprietary medicines which are, in the great majority of instances, nothing but pure frauds. The drugs are expensive and the people waste their earnings in buying them besides oftentimes irreparably injuring their health. The general practitioner should study these reports so that he may clearly point out to his patients the folly and danger of using medicines and preparations which may lead to drunkenness, the opium or cocaine habit, or render operations as in the case of cancer quite impossible from the delay caused by using these quack remedies in the hope of a cure. With the help of such authoritative publications little by little the laity will learn that the advice of a good physician is worth far more than a bottle of medicine bought at a drug store, which has nothing to recommend it except false and lying statements made by its manufacturer.

International Clinics. Edited by Henry W. Cattell, M. D. Vol. I. Twentieth Series, 1910. (*Philadelphia and London: J. B. Lippincott Company.*)

Three papers on the serum diagnosis of syphilis, one of them by Hideyo Noguchi, who is known for his special work on this problem, two on pellagra, with excellent illustrations, and one on purin metabolism, show how successfully the editors succeed in keeping these clinics up-to-date. Men working in different specialties will find other papers to interest them.

Living Anatomy and Pathology. The Diagnosis of Diseases in Early Life by the Roentgen Method. By Thomas Morgan Rotch, M. D., Professor of Pediatrics, Harvard University. Illustrated. 1910. (*Philadelphia and London: J. B. Lippincott Company.*) Price, $6.

This handsome work, dedicated to Dr. William Osler, is a most valuable contribution to pediatric literature, and no student of children's diseases can well afford to be without it. The collection of X-ray photographs is unique and a careful study of them will repay any physician. These illustrations show normal and diseased conditions from the first to the sixteenth year, supplemented by brief explanatory notes, and longer chapters dealing with the diseases of the different portions of the body described. No other work of the kind exists, and this one will always remain an authority, for it can be improved only by further additions. Dr. Rotch is to be congratulated and complimented on presenting the profession a work of such importance.

Pye's Surgical Handicraft: A Manual of Surgical Manipulations, Minor Surgery and Other Matters Connected with the Work of House Surgeons and Surgical Dressers. Fifth edition. Revised and largely rewritten by W. H. Clayton-Greene, F. R. C. S., etc. Illustrated. (*Bristol: John Wright & Sons, Ltd.; London: Simpkin, Marshall, Hamilton, Kent & Co., Ltd., 1909.*)

In the preface to the first edition published in 1884 the author says he has endeavored to describe the details of surgical work as it appears from the point of view of house surgeons and dressers in surgical wards.

In the revised edition an attempt has been made to maintain the character and style as originally adopted by Mr. Pye, and the reviser says that it has been his aim to complete a book which will cover most of the common details and complications of treatment occurring in the course of surgical practice.

The book is divided into ten sections as follows: 1, Of the Arrest of Hemorrhage; 2, Of Apparatus for Restraint and Support (Bandages, Splints, etc.); 3, Of Fractures, Dislocations and Sprains; 4, Of Wounds, Ulcers and Burns; 5, Of Cases Requiring Prolonged or Mechanical Treatment; 6, Of Minor Surgery and Kindred Subjects; 7, Of Special Cases Connected with the Head and Throat; 8, Of Certain Emergencies, Surgical and General; 9, Of the Administration of Anæsthetics; 10, Miscellaneous.

The chapter on Minor Surgery of the Eye is written by L. Paton; those on Head Injuries and Diseases of the Nose and Throat, Larynx and Ear, by W. H. Carson; The Treatment of

Cases of Poisoning and on Urine Testing, by W. H. Wilcox; Anæsthesia, by J. Blumfeld; and X-rays, by G. A. Simmons.

There are numerous illustrations, many practical suggestions, and the book is nicely gotten up. The descriptions are necessarily brief, but are for the most part clear.

This little hand-book will be more useful to house surgeons and surgical dressers, as originally intended by Mr. Pye, than to the operating surgeon.

J. S. D.

Immunity and Specific Therapy. By W. D'Este Emery, M. D., B. Sc. (Lond.), etc. Illustrated. (*New York: Paul B. Hoeber, 1909.*) Price, $3.50.

The author states in the preface that he has "attempted to give a connected and symmetrical outline of the chief facts definitely known with regard to the method in which the body protects itself against infections, and of their applications in the diagnosis, prevention and treatment of disease."

The text is preceded by an excellent glossary which serves a very useful purpose since many of the newer terms introduced in the recent studies in immunity are not defined in the ordinary medical dictionaries.

In the introductory chapter the author defines immunity and discusses the immediate and predisposing causes of infection and gives a brief historical review of the earlier theories of immunity.

The nature of toxins, the phenomena of antitoxin formation, the origin of antitoxin, and immunity to toxins are dealt with at considerable length and on the whole in a satisfactory manner, including a brief review of Ehrlich's Side-Chain Theory.

This arrangement is a fortunate one, as the toxin-antitoxin reaction is one of the simplest and at the same time one of the most studied and perhaps best understood of the immunity reactions and going into detail, as the author does with this subject, prepares the way for the more complex reactions which follow.

It would seem a more logical sequence to have followed the chapters on toxin and antitoxin by a consideration of agglutinins and precipitins instead of, as the author has done, chapters on Bacteriolysis and Allied Phenomena.

Bacteriolysis and hemolysis are well treated and the conflicting views of Bordet and Ehrlich concerning the action of immune body and the unity or plurality of complement are fairly stated and much of the experimental evidence which each brought forward in support of his views is given, although it will perhaps be difficult for one unfamiliar with the subject to follow the intricacies of the experimental data and interpret intelligently the results.

The author very reasonably calls into question some of the evidence which has been brought forth for the existence of anti-complement.

The chapter on agglutinins is satisfactory and the discussion of the physical laws which may play some part in the phenomenon of agglutination is very interesting.

Precipitins are dealt with briefly and some very interesting phenomena in connection with them are omitted.

Phagocytosis is given lengthy consideration, largely from the standpoint of a partisan of Wright's opsonic theory.

In view of the great practical importance of the tuberculin reaction it is to be regretted that a more comprehensive exposition of this subject is not given.

The chapter on the Colloidal Theory of Antibodies is of great interest and is evidence of the present trend of immunity researches along physical and physico-chemical lines.

The text closes with a chapter on Practical Applications which consists largely in an exposition of vaccine therapy controlled by Wright's method of opsonic determination. The author frankly admits that in many cases the results are disappointing.

A very comprehensive and useful bibliography is given by chapters at the conclusion of the book, together with an index of authors cited and a subject index.

The books fills a much felt need and is the most comprehensive systematic treatise of the subject in English with which the reviewer is familiar.

A most serious fault is the great number of textual errors in which the book abounds. Such errors, for example, as the use of the word "leucocytes" where the word "bacteria" should have been used, "serum" for "corpuscles," "toxin" for "antitoxin," etc. In some places the mistakes are evident, but in others they would probably lead to utter confusion in the mind of one not already familiar with the subject.

These unfortunate errors will doubtless be eliminated in subsequent editions and it is to be hoped that the more recent work on the mechanism of cobra-venom hemolysis, and a fuller discussion of the Wassermann reaction and the subject of anaphylaxis will be included.

W. L. Moss.

Nervous and Mental Disease. Monograph Series No. 6. Epidemic Poliomyelitis. Report of the Collective Investigation Committee on the New York Epidemic of 1907. (*New York: The Journal of Nervous and Mental Disease Publishing Company, 1910.*)

This admirable report is divided into five chapters, preceded by a brief introduction: I, Epidemiology of Poliomyelitis, by Drs. Boldman, Ager and Terriberry; II, On the Conditions Preceding Onset and the Early Symptoms of the Disease, by Drs. La Fétra and Schwarz; III, The Symptomatology of Epidemic Poliomyelitis, by Drs. Clark, Hunt, Jelliffe, Sachs and Zabriskie; IV, The Pathology and Pathological Anatomy of Epidemic Poliomyelitis, by Drs. Flexner and Strauss; V, Treatment of Poliomyelitis, by Drs. La Fétra, Jelliffe, Ager, Taylor and Sachs.

As is seen from these headings, the disease has been considered from the principal points of view, and each chapter prepared by capable subcommittees, with the result that this report must be carefully studied by all who desire to be masters of the subject of poliomyelitis. It is a report to appeal to both general practitioners as well as specialists in nervous diseases. The committee as a whole presents this clear, concise and thorough work which helps to throw light upon many conditions in the disease which have been obscure, and has made a really valuable contribution to the literature of an important disease.

Modern Surgery: General and Operative. By J. Chalmers DaCosta, M. D., Professor of Surgery and of Clinical Surgery in the Jefferson Medical College, Philadelphia. Sixth edition, greatly enlarged. Illustrated. (*Philadelphia and London: W. B. Saunders Company, 1910.*) Price, $5.50.

What was said favorably of this work in the February, 1908, number of this journal applies with still greater force to the sixth edition. The author by his frequent revision does not allow this successful surgery to become a work of the past, but by his additions and alterations makes it of still greater use to students and practitioners. The author forestalls criticism by his own regret and apprehension at the growth of the work. In the next edition perhaps he may be able to demonstrate his well-known surgical ability by removing certain portions of his "subject," so treating him that he is better after the operation than he was before. The excellence of DaCosta's work will make this difficult.

Some Common Remedies and Their Use in Practice. By Eustace Smith, M. D., F. R. C. P., etc. (*New York: Paul B. Hoeber, 1910.*) Price, $1.25.

This small book is composed of "reprints of papers contributed to The British Medical Journal," and any practitioner who will read them with care and appreciation will get many valuable hints from them as to the correct and most effective method of prescribing certain drugs. They are admirable clinical lectures, and it is only a pity that there are not more of them. The seven chapters are entitled as follows: 1, On an unjustly neglected

remedy (tartarated antimony); 2, On the internal use of the oil of turpentine; 3, On the use and misue of iron remedies; 4, On the use of alkalies in practical medicine; 5, On antispasmodics and the care of spasm; 6, On some uses of opium; and 7, On the use of sodium salicylate in certain serous inflammations.

The Conquest of Disease Through Animal Experimentation. By James Peter Warbasse, M. D., etc. (*New York and London: D. Appleton Company, 1910.*)

It is to be hoped that this defence of animal experimentation may find its way where it will be serviceable, but unfortunately the author's ability to write a useful work on this subject is not as marked as his zeal in the cause. The book cannot be compared in value to Stephen Paget's more extensive work on this subject published a few years ago. There is some danger that this book will prove more advantageous to the antivivisectionists than to the defenders of experiments on animals, for some statements made are too sweeping, and it is carelessly written.

Ophthalmic Surgery. By Charles H. Beard, M. D., etc. Illustrated. (*Philadelphia: P. Blakiston's Son & Co., 1910.*) Price, $5.

In this book are described practically all the operative methods adopted in present-day operative surgery on or about the eye. Much space is devoted to the subject of tendon advancement operations in the case of squint, and a full description of the tendon lengthening operation, as proposed by Stephenson, of London, is given. Considerable space is also given to the consideration of operations for ectropion, entropion, symblepharon and ptosis. It is probably just as well that we have a book in which descriptions of various methods of doing those operations are gotten together, although most operators will merely receive suggestions from them and adopt a more or less original means of dealing with their own cases. The operations spoken of above are described with very much more fullness than in the ordinary text-books, but in the description of the more important and certainly more frequently performed operations, such as cataract extraction, probe passing, iridectomies for glaucoma, and the rather important lid tumor operations, there is not the authoritative tone met with in less pretentious books. To anyone devoting much attention to plastic surgery about the eye, this book would probably be of interest, but as a whole it is not a volume of great merit. Making extravagant statements to drive an idea of the author home, such as: "Lack of aseptic precautions oft turns into *abject failure* the most *brilliantly executed* surgical measure, while attention to them can make a *perfect triumph* of a *wretched bungle*" (page 1) and "It is *becoming so universal* for ophthalmic surgeons to be *ambidextrous* that it now looks almost like a confession of inferiority for one to stand at the left side of the patient, for instance in making a corneal section for cataract in the left eye" (page 114), is an unpardonable fault in a medical work. The descriptions are not always clearly written, and the grammar is often bad.

B. B. Browne.

Diseases of the Heart. By James Mackenzie, M. D., M. R. C. P. Second edition. (*New York: Oxford University Press, American Branch, 1910.*)

The fact that one edition of this book has been exhausted within a year is gratifying evidence that the medical public has awakened to the importance of graphic methods in the study of cardiac diseases. The particular value of the book lies in the fact that the author has made careful physiological studies upon more patients than any other writer in the history of medicine. Like the first edition of the book, the second is not a text-book of heart diseases, but deals entirely with the author's own studies upon the venous pulse, illustrated with an unparalleled wealth of original tracings.

The author says, "The interpretation of these tracings represents the present state of my knowledge," and with exceptional liberal-mindednes writes, "Should other investigators prove these interpretations wrong by the discovery of new facts, I shall rejoice with them." However, since both editions contain the statement that the carotid origin of the *c* wave "is the main, and for practical purposes the only one, that need be considered," it must be admitted that he does not deem any work contradictory to his own as worthy of a hearing, even when the majority of clinical and experimental observers side against him. Such dogmatic statements are found throughout the book, often at the expense of scientific accuracy. The author has made little attempt to present the experimental evidence upon which interpretations of the venous pulse are based. He still invokes the "nodal rhythm" (impulses arising in the atrio-ventricular bundle) to explain all forms of disturbed rhythm in which there are no signs of auricular contraction.

The fascinating conversational style is retained and renders the book easy reading, but one often regrets that the author has made no attempt to analyze and tabulate his vast number of carefully studied cases for the benefit of the reader, and that he does not bring the cases of functional disturbances which he has studied so carefully into closer relations with the chapters on prognosis and treatment. One would naturally expect that in a work of this kind the pathological and prognostic significance of extrasystoles and of the absolute arrhythmia would be discussed in sufficient detail to enable the reader to view his own cases in the light of Mackenzie's experience; and that, if absolute assertions were not warranted, at least a statistical summary of the author's cases might be given. Unfortunately, however, this has not been done; and the reader is left to shift for himself or to rely on the facts revealed by simple physical diagnosis in the handling of his own cases; so that, in some ways the book blights the very hopes which it has aroused, though never the interest which it has awakened.

Most of the remarkable statements found in the first edition are perpetuated with equal positiveness in the second. Treatment is dealt with a little more fully than in the first edition. The Spa tratment is characterized chiefly as a "holiday," and the effect of CO_2 baths is not even considered. The restriction of salt in diet is briefly designated as "foolish." On the other hand Mackenzie gives a very interesting account of his own studies upon Hill's oxygen inhalation with a tight mask. The chapter on digitalis deals chiefly with the changes in rhythm due to over-doses rather than with the effect of the drug in therapeutic doses. One is surprised to find that the most modern phase of cardiac treatment, the intravenous strophanthin injection, is still unmentioned.

An excellent short chapter, by Thomas Lewis, upon the electrocardiogram, constitutes one of the great improvements in the new edition, though Mackenzie does not incorporate this phase of the subject in his own discussions. Blood pressure observations are often mentioned, but the important studies with the X-rays and the graphic studies upon the heart sounds are still ignored, so that the author cannot lay claim to any completeness in presenting the modern aspects of heart diseases, but only of having presented one phase of them.

The second edition is printed on lighter paper than the first, making it a thinner volume in spite of the greater number of pages. The reduction in price is also certain to improve its sale.

A. D. H.

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CONTENTS.

A UNIQUE COINCIDENCE OF MULTIPLE SUBCUTANEOUS HÆMANGIO-ENDOTHELIOMA, MULTIPLE LYMPHANGIO-ENDOTHELIOMA OF THE INTESTINAL TRACT AND MULTIPLE POLYPI OF THE STOMACH UNDERGOING MALIGNANT CHANGES; ASSOCIATED WITH GENERALIZED VASCULAR SCLEROSIS AND CIRRHOSIS OF THE LIVER.

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AND

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(From the Medical Service and Pathological Laboratory of the Johns Hopkins Hospital.)

Introduction.

The basis for the following histological studies with the theoretical deductions appended is found in a case which has been under clinical observation for the past three years. This showed such unusual features during life that we undertook an exhaustive investigation of the tissues at autopsy.

The material will be presented in the following order:

1. Description of the case.
2. Protocol of the autopsy.
3. Histological studies.
4. Summary and theoretical deductions.

Clinical History.

T. H., male, mulatto, 65 years old. Ship's cook. Born in Hindustan. Was admitted to the Johns Hopkins Hospital, November 17, 1906. Medical number 20,395.

Complaint: "Swelling of stomach."

Family History: Unimportant.

Personal History: Patient had measles as a child, smallpox at 9. He does not recall having had any other diseases in childhood. Has never had typhoid fever, pneumonia, or pleurisy.

No cardiac or respiratory symptoms.

Gastro-Intestinal: Patient has always had a good appetite. His bowels have moved once a day regularly. He has never had any colic or pain in the abdomen. About 20 months ago, after quitting drink, he began to have occasional attacks of vomiting in the morning. The vomitus was yellow and tasted very bitter. He has had similar attacks (one every 2 to 3 weeks) up to the present. Has not noticed blood in his stools.

Urinary: Patient has slight nycturia, but never has had any burning or pain on micturition. Patient denies having

had syphilis and gives no definite history of a hard or soft chancre. No history of secondaries. Gonorrhœa at 17.

Skin: Patient has never been jaundiced. He has never had any skin eruption, or itching.

Extremities: No ulcers on legs. No pain in joints or bones.

Habits: Patient's work has always been light—cooking on shipboard, and serving in army and navy. *Alcohol:* Up to two years ago patient was a steady drinker. When on shore he drank 3 to 4 glasses of beer a day and half a pint to a pint of whiskey. He got no liquor while at sea, but went on a spree whenever in port. Two years ago he quit drinking entirely, and has not used alcohol since. *Tobacco:* Practically none.

Present Illness: About 3½ months ago, while working in a store, he noticed swelling of the feet. At this time he had to walk a great deal. The swelling got worse during the day, but subsided at night. Gradually his "stomach" became swollen, and the œdema of the legs remained constant. About 2½ months ago he quit work for a week or so, rested, and took large doses of Epsom salt. He states that his stools were of clear, watery fluid. The ascites subsided, and he went back to work, at which he continued till 10 days before admission. His only symptom has been abdominal swelling. His bowels have moved once a day. A few times he has vomited a little bitter yellow fluid in the morning. This contained no blood. He has not noticed any blood in his stools. His appetite has been good. His micturition has been as usual. He has had no palpitation or shortness of breath till recently, when he has had dyspnœa on exertion. He has had no cough. Has not lost weight.

Physical Examination: The patient is a light mulatto, sparely nourished. There is no exophthalmos. Pupillary reactions are normal. Gums and mucous membranes show slight cyanosis. Thyroid isthmus is slightly enlarged; the lobes are barely palpable. Lymphatics of the neck seem normal. Respirations are shallow and costal in character; expansion is limited on both sides. Percussion note is hyper-resonant over the upper lobes in front with dulness low in the axillæ and in both backs. The breath sounds are harsh and clear over the upper lobes, diminishing over the impaired area and accompanied by numerous fine moist râles on forced inspiration. No evidence of fluid in the pleura.

Heart: Displaced upward. Point of maximum pulse in 4th left interspace 10.5 cm. from mid line. Dulness reaches 13.5 cm. to left in 4th interspace and above to 1st interspace, 2.5 cm. to right in 3d interspace. The heart sounds are clear and regular and of normal intensity. The pulse is 80, regular in force and rhythm, of moderate tension, with very marked sclerosis of the peripheral arteries.

Abdomen: The abdomen is very tense and swollen; its skin is shiny. The superficial veins are enlarged, especially those along the lateral margins. There is no caput medusæ. Epigastric veins are not prominent. Umbilicus is protruding. Fluctuation wave is definite. Liver not palpable. Spleen not felt. There is movable dulness on percussion. The liver dulness begins at the 3d rib and extends to point 3.5 cm. above the costal border in the right mammillary line. The girth of the abdomen at umbilicus is 106 cm.

Genitalia: Normal except for an atrophic undescended left testicle.

Extremities: There is marked clubbing of the fingers and toes. There is œdema of the thighs and legs. The knee kicks are normal. Plantar response is normal.

Nov. 19: Abdomen tapped and 7.5 litres of straw-colored fluid removed from the abdominal cavity. Nothing remarkable about the appearance on microscopic examination of this material. The cellular elements were few. Specific gravity, 1011; albumin, 6.6 grams per litre.

Blood: Showed secondary anæmia. R. B. C., 4,492,000; W. B. C., 5400; Hb., 82 per cent.

Differential Count: Showed slight reduction of the polymorphonuclears and small mononuclears. Slight increase in large mononuclears and transitionals.

Patient was much relieved by the removal of the ascitic fluid. The edge of the liver could not be made out definitely. Spleen was not palpable.

Patient was tapped again on Nov. 30 and 5.5 litres removed. From this time he gradually improved and was discharged Dec. 17, 1906.

2d admission, March 23, 1907: Patient was readmitted in much the same condition as before. In the three months since he left the hospital he had been unable to work and has had some occasional morning vomiting and gradually increasing ascites, anasarca, and dyspnœa.

Physical Examination: Is practically as on first admission, except that on admission it was noted the peripheral arteries, generally, and the veins, as well, were very greatly thickened. The anæmia had somewhat increased, hæmoglobin being 62 per cent, 5000 white cells, and 4,000,000 red cells. The great distension and dyspnœa were relieved by tapping and removal of 10 litres of ascitic fluid.

After repeated tappings, patient's condition gradually improved. The edge of the liver is noted as palpable on June 10, small, smooth and hard.

Patient was discharged on June 15, somewhat improved.

3d admission, Sept. 16, 1907: Patient was confined to his bed much of the time between his discharge from the hospital and readmission with the same symptoms as before; marked ascites, swelling of the legs, dyspnœa, occasional nausea and vomiting. No blood in the vomitus nor stools.

Physical Examination: Practically as on previous notes, except for some increase in cyanosis. The girth was 112 cm. on admission; 86 cm. after tapping and removal of 11 litres of straw-colored fluid. Character of the fluid practically the same as previously noted.

Dr. Emerson, Nov. 14: A few small nodules along the right forearm which suggest phleboliths; not attached to any vein.

The edge of liver is distinctly palpable after tapping. The liver seems very small. The lateral abdominal veins are large with a distinct upward current in them. There is a slight enlargement of both parotid glands.

On Dec. 19 it is noted that the skin on the lower arms

shows marked wrinkled lines suggesting ichthyosis. A small firm subcutaneous nodule is found above the left scapula.

Patient discharged at his own request, slightly improved, Dec. 19, 1907.

4th admission, Feb. 3, 1908: Patient spent the intervening time in bed. Has been very comfortable. The increase in ascites and shortness of breath forced him to return to the hospital.

Physical Examination: Practically as in previous admissions.

Dr. Thayer: Increase in the clubbing of the fingers, palpable small liver and enlarged spleen. Parotid enlargement increased. Moderate dilatation of the superficial veins of the abdomen and thorax. No *caput medusæ.*

Patient improved under treatment after repeated tappings and was discharged on April 21, 1908.

Diagnosis: Cirrhosis of the liver (atrophic).

5th admission, June 16, 1909: In four weeks, since his discharge, patient has gradually become œdematous and the ascites is very marked. Some dyspnœa and morning vomiting.

Physical Examination, Dr. Clough, June 18, 1908: Emaciated. Skin dry, scaly, of a peculiar chocolate color. Scleræ distinctly jaundiced. Marked arcus senilis. Mucous membrane of mouth distinctly pale.

Lymph glands are somewhat enlarged, firm and shotty throughout. Both epitrochlears felt.

Chest flaring. Movements rather shallow and restricted. Lungs clear throughout on percussion. Breath sounds vesicular throughout. Numerous crackles at bases and lower axillæ.

Heart: Displaced upward. Sounds clear throughout, normal in character.

Pulse regular, fair in volume, tension not increased. Brachial and radial arteries markedly tortuous, visible; diffusely sclerotic.

Abdomen: Much distended, bulging in flanks. Veins are distended. On palpation very tense—nothing can be felt. No tenderness. Marked fluctuation wave. On percussion, tympany in epigastrium and upper abdomen. Movable dulness in the flanks.

Legs are moderately œdematous.

Oct. 27, 1908: R. B. C., 4,270,000; W. B. C., 8600; Hb., 53 per cent.

Dr. Boggs, Nov. 3, 1908: Scattered along the inner aspect of right upper arm and forearm, and somewhat on ulnar side of forearm, are several subcutaneous nodules, of fairly uniform size, averaging about 5 mm. in diameter. They are quite firm in consistency, the skin moves freely over them, and they are more or less adherent to the fascia, though some of them can be picked up in fingers and moved freely. No pain on pressure over them. On stretching the skin tightly over them, they are seen, in good light, to have a faint blue color, similar to that of the veins. There are a very few similar nodules on the left forearm, mostly on its ulnar aspect; none on the upper arm. There are a few, also, scattered about the back, at the right scapular angle and along the spine. No nodules felt in skin of lower legs.

Dr. Boggs, Nov. 18, 1908: The larger subcutaneous nodules noted in the arms, apparently have pulsation on picking them up. The subcutaneous tissue in lower leg is somewhat œdematous and no nodules can be made out. About the poplitcal space on both sides are a few small nodules, corresponding in size and texture to those noted in the arms. No nodules made out in the back, which is œdematous.

On costal border are two small angiomata symmetrically placed, just above costo-chondral articulation of 6th rib on each side.

Dr. Boggs, Dec. 24, 1908: The subcutaneous angiomata have increased in size especially on right forearm. Under local anæsthesia an attempt was made to excise one of the subcutaneous nodules at junction of mid and lower third of right arm. On exposure it seemed to have a deep purple color and lay parallel and in close relation to a small cutaneous artery. On attempting to free it from surrounding tissues, the capsule was punctured and the small tumor collapsed, leaving an actively pulsating arterial lesion. This wound was closed, as the tumor could no longer be recognized, and a second node on inner side of elbow was excised with artery lying parallel to and supplying it. It was placed in Zenker's fluid for microscopic examination. This mass, when exposed, seemed to be a direct offshoot of a very sclerotic artery.

Dr. Boggs, Feb. 3, 1909: The small angioma, which collapsed on attempted excision Dec. 24, has filled up and presents the same picture as before. The number of nodules somewhat increased, especially along extensor surface of forearm on both sides.

Dr. Boggs, April 21, 1909: Patient continues to fill up rapidly after tapping. General condition otherwise much the same. The clubbing of fingers is perhaps more marked than on admission. Wassermann reaction, negative.

Dr. Boggs, June 5, 1909: The subcutaneous angiomata are increasing in size and number on both arms. A new one, in the right hand at middle of the ulnar margin, shows some redness in skin over it. Another, not previously noted, at base of first finger and near it a marked ecchymosis.

Patient's general condition is very much as in last note. Parotid glands are rather more swollen, have a soft induration, and are not tender.

Dr. Brotherhood, June 10, 1909: 33d tapping. 9 litres of straw-colored fluid removed, slightly cloudy. Reaction neutral. Specific gravity 1012. Albumin—Esbach, $3\frac{3}{4}$ grams per litre. Microscopically—contains few endothelial cells, few mononuclear leucocytes.

Dr. Boggs, June 21, 1909: Few scattered subcutaneous nodules on the legs similar, on palpation, to those noted on the arms, but smaller. One or two small ones felt about popliteal spaces on both sides.

Dr. Sladen, Aug. 5, 1909: To-day there are two fairly good-sized nodules just over right zygoma, not previously noted. Two new ones on right wrist, and over arms and face are many small red macules from which the blood is easily expressed, which suggest new formed angiomata.

Dr. Futcher, Sept. 10, 1909: Patient has not been so well for the past few days. The bowels, which have been rather

loose throughout, have been more so in the past three days, as many as ten stools a day. Forearms, particularly over the ulnar aspect, present numerous subcutaneous visible and palpable nodules, ranging from 0.5 to 1.5 cm. There are probably 20 to 30 on each arm. Skin is movable over them and they are movable on subjacent structures. They appear to be situated chiefly along the course of subcutaneous veins, often being observed at junction of two veins. They are fairly firm —do not diminish materially in size on pressure.

Dr. Boggs, Sept. 13, 1909: Emaciation has progressively increased. The angiomatous nodules under skin of arms have increased in size and number, and color shows through skin. Many of them have a reddish-purple tint. Forearms are quite thickly studded with these nodules. A few are found on wrists and dorsa of the hands—none on the fingers. There has been no appreciable increase in number of the nodules about the shoulder girdle. None are found on the back. A few small ones are found about the iliac crests and over the sacrum, which were not noticeable eight weeks ago. There are a few of these similar nodules, quite small, but palpable, on the inner side of the thigh along the course of superficial veins. There is a group of nodules, not larger than wheat grains, just below the popliteal space and a few along the course of the long saphenous vein on the right side. On the left leg the nodules in the thigh are slightly more numerous than on the right, and larger. Distribution on the left leg is quite similar to that on right. None made out on dorsum of foot.

Dr. Boggs, Oct. 6, 1909: The number of the subcutaneous nodules is increasing, the skin over some of the larger is becoming more atrophied, and color shows through quite distinctly, either reddish or purplish. The small nodules on legs are also increasing in number and size. General condition otherwise much as before.

Oct. 16, 1909: Abdominal tapping No. 43. 8150 cc. of pale yellow, turbid fluid removed. Specific gravity 1008. Reaction neutral. Albumin 6 grams per litre. Endothelial cells, with eccentric nuclei and granular cytoplasm.

Blood Examination, Oct. 22, 1909: R. B. C., 3,940,000; W. B. C., 11,800; Hb., 50 per cent.

Dr. Boggs, Dec. 12, 1909: Patient has gradually sunk into coma with respirations taking on a true air-hunger type. The ascites has disappeared. The skin is wrinkled and loose over the abdomen. There is œdema of the hands and dependent portions of the body, moderate in grade, with numerous subcutaneous hæmorrhages into deeper layers of the skin, varying from petechiæ of small size to several centimeters in diameter. Breath has rather a fruity odor. The dessicated condition of the skin has brought into prominence some small nodules not previously noted, having the same character as those described on the arms. There are several masses on the face above the zygoma, above the tragus, a third just below the right malar; none made out on left side of face.

Some impairment of respiration movements in both bases behind and deep inspiratory movements are accompanied by showers of rather dry râles. Nowhere is any tubular breathing made out. Along the left border of the heart there are showers of dry crackling râles at the end of inspiration. Heart sounds are distinct and feeble.

Liver dulness begins at rib vi, extends only about 4 cm. in mammillary line. Neither liver nor spleen is felt. Small subcutaneous nodules, noted in legs, have increased in size, apparently involving the skin, and differ from others in showing fine radiating vessels about margin, of bright red color. They are very hard and shotty. There is slight œdema of thighs and also of lower leg. The ichthyosis is very marked.

Dec. 15, 1909: The coma persisted and the patient became gradually weaker and died at 9.10 a. m.

During this last admission 432 litres of fluid were drawn from abdomen in 47 tappings. This represented a protein loss of 260 grams.

Diagnosis: Atrophic cirrhosis of liver; multiple subcutaneous hæmangiomata; ichthyosis simplex. Chronic gastritis and colitis.

Autopsy.

T. H., aet. 67 years. Ward M. Died 9.10 a. m., Dec. 15, 1909. Autopsy (No. 3310) 9.30 a. m., Dec. 15, 1909. Dr. Winternitz.

Anatomical Diagnosis: Cirrhosis of liver; ascites; chronic proliferative peritonitis; collateral circulation established through the diaphragm to the lungs and through the omentum to the parietal peritoneum; arterio-sclerosis with diffuse dilatation of the aorta and thrombus formation; sclerosis of the peripheral arteries and veins with multiple subcutaneous and visceral hæmangiomata undergoing malignant change (endothelioma); multiple lymph-angiomata of the intestine and stomach undergoing similar change; chronic gastritis with multiple polypi undergoing carcinomatous degeneration; chronic fibrous myocarditis; pulmonary emphysema; chronic fibrous pleurisy; chronic interstitial and peri-splenitis; chronic diffuse nephritis.

Only those portions of the protocol which have a bearing upon the subsequent investigations will be given in detail.

Body: Is that of a somewhat emaciated mulatto man, 173 cm. in length. Rigor mortis has not yet set in, and there is no lividity even in the dependent parts. The face is somewhat emaciated and both temporal fossæ are conspicuous and the orbits are somewhat depressed. The conjunctivæ are slightly pigmented about the periphery of the corneæ. The pupils are equal and measure about 4 mm. in diameter. There is a slight arcus senilis. The thorax is barrel-shaped. The abdomen is scaphoid. The veins over the abdomen are rather more prominent than normal. In the median line beneath the umbilicus is a non-pigmented scar-like area.

Perhaps the most noteworthy thing on external examination is the presence of numerous small, subcutaneous nodules (Fig. 1); these have been described in detail in the history. The nature of these nodules in general is as follows: They are elevated and vary somewhat in their consistence, some being extremely firm and shot-like; others not quite so firm, and a few can be decreased markedly in size on pressure. They are

all of them freely movable on the underlying tissue. In a few the skin is slightly adherent. These tumors vary in size; the largest ones measuring about 1 x .75 x .75 cm., while small ones occur which are almost miliary in size. Their distribution is somewhat as follows: On the right side of the head just above the zygoma; in the region of the temporal veins above the orbit; beneath the malar process; and a small one just anterior to the tragus. The left side of the face seems to be free from tumors, and none are to be made out in the neck. On the trunk the tumors are scanty and irregular. There are none on the anterior wall and axillæ with the exception of a single node in the middle of the left upper abdominal quadrant. On the back there are a few nodules about the right scapula and some large ones in the sacral and gluteal regions. Scattered over the arms and legs, in general parallel to the course of the subcutaneous vessels, are many nodules, the larger being confined to the upper extremities, while those in the legs are somewhat smaller and softer. The relation of these tumors to the vessels can be much more distinctly seen on subcutaneous examination. On reflecting the skin there is found an extreme diffuse thickening of the subcutaneous veins. Over the outer half of the elbow and the upper third of the forearm a number of small, nodular masses are found lying in the superficial fascia. These masses correspond in general appearance to those previously excised and described during life and vary in size from about 6 x 4 x 3 mm. to scarcely more than a pin-head. The larger ones are dark red in color and firm in consistence, having a well-defined capsule. The smaller are rather translucent, very much paler in color and firmer in consistence. Although these are very superficial in position they have nowhere invaded the skin proper, and in some places the injection[1] of small capillaries in the skin over the tumors involves the capsule of the tumor, but not the tumor itself. In position these masses have a striking relation to the small branches of the superficial veins. In general they lie parallel to the larger veins and small branches diverge toward them from these trunks. At one point, where the deep layer of fascia has been cut, a small tumor nodule is found lying in the fascia between the muscles, but not invading the muscle.

Abdomen: Contains an excess of clear yellowish fluid. The omentum is rolled up, thickened, and extensively adherent to the parietal peritoneum, especially in the left upper quadrant, and the adhesions are almost entirely composed of vessels averaging 2 to 3 mm. in diameter. Numerous hæmorrhagic areas are scattered through the omental fat. The dome of the right lobe of the liver is adherent to the diaphragm by strong fibrous bands in which are a number of large vessels. These latter penetrate the diaphragm and anastomose with vessels in a mass of pleural adhesions. The spleen is firmly adherent to the diaphragm and to the stomach. These adhesions are dense and in some places calcified. The stomach is small, extending only a short distance below the costal margin. The parietal peritoneum is considerably thickened and shows numerous dilated vessels. Otherwise the abdomen and pelvic viscera are normally disposed.

Thorax: The ribs are brittle, with thin walls, large spaces and little marrow. The pleural cavities are almost obliterated by rather old fibrous adhesions which are easily separated. There is no excess of fluid. The pericardial sac is normal.

Heart: Weight 270 gms. Presents nothing of note.

Lungs: In addition to the pleuritic adhesions above noted, the principal point of interest is the marked sclerosis of the pulmonary vessels which involves not only the large trunks, but even the smaller vessels which stand out conspicuously on section.

Spleen: Shows a thickening of the fibrous trabeculæ and marked general sclerosis of the vessels.

Stomach: Is contracted; the pylorus is thickened and resembles the external os of the uterus. On opening the stomach along the greater curvature a remarkable condition is disclosed (Fig. 2). The surface is covered with a blood-stained mucous exudate and is everywhere studded with polypus-like masses of varying size. The mucosa, as a whole, is of a deep red color except along the upper portion of the lesser curvature. The discoloration is intensified in the mucosa covering the polypi. These polypi vary greatly in appearance, showing every gradation from small sessile masses 0.5 cm. in diameter to those having a definite stalk and a cauliflower-like extremity, some of which have a diameter of 2 to 3 cm. Some of the largest nodules show no pedicle. Such a group is found in a circular arrangement near the cardiac orifice. The periphery of this circle is composed of several nodules which are in intimate contact. In the center is a crater-like depression which is covered by an unbroken mucosa. The extreme diameter of the mass is about 6 cm., height 2 cm., and the diameter of the crater about 3 cm. Section through the polypus-like masses shows them to be for the most part quite superficial, only involving the mucosa and submucosa. The cut surface of these is reddish, mottled by small translucent cysts and grayish white, more opaque areas. In several nodules, especially those above described in the region of the cardia, this grayish-white tissue composes the entire polyp. In two of these the underlying muscularis is thickened and firmer in consistence, with translucent or colloid strands invading and separating the muscle bundles; this involvement of the muscularis extends only about 2.5 cm. beyond the bases of these polypi.

Intestines: The peritoneal surface of the intestine is not uniform, but thickened here and there by small milky patches. Many small nodules may be felt in the wall of the gut. On opening the intestine along the mesenteric border the mucosa is everywhere covered with blood-stained exudate. The rugæ are prominent and somewhat œdematous. The entire intestinal wall is beaded with nodules. Some project slightly and are covered by a darker red mucosa. On transillumination it is seen that these nodules are innumerable and occasionally

[1] In order to study the relation of the nodules to the blood-vessels, an injection of Berlin-Blue was begun within twenty minutes after death. Fluid was forced into the left brachial artery under 200 mm. Hg. pressure, the excess being allowed to drain from the cephalic vein. The injection continued for two hours.

arranged in chains following the long axis of the bowel. In many places they are confluent. They are seen to lie at different levels in the intestinal wall, some, as above described, just beneath the mucosa, others near the peritoneal coat, showing through as pale brownish spots. About these latter small vessels radiate in the peritoneum. The individual nodules vary from 2 to 6 cm. in diameter. On section these nodules are sharply defined, rather firm in consistence, and have a pinkish-brown color. It is of interest to note the presence of these nodules in the œsophagus, duodenum, throughout the small and large intestine, and as subsequently shown on histological examination, also in the stomach.

There were no gross abnormalities in the mesentery.

Liver: Measures 21 x 15 x 9 cm. and weighs 1070 gms. The surface of the liver is very irregular and nodular. The capsule is delicate except at the point of origin of the vascular adhesions above described. The vessels in these fibrous bands have extremely thick sclerotic walls. The liver is firmer than normal. On section the normal architecture is absolutely obliterated and coarse bands of fibrous tissue divide the liver into false lobules of varying size. Small areas of semi-translucent, brownish liver tissue are seen throughout, while most of the tissue between the fibrous bands is yellow and opaque. Here and there small islands of regenerating liver tissue project from the cut surface. These are circumscribed, pale brownish in color, and not involved by the fibrous overgrowth.

Pancreas, Adrenal, Pelvic Organs: Present nothing noteworthy.

Kidneys: The blood-vessels are everywhere prominent as a result of a thickening of their walls. There is also a slight increase in connective tissue.

Blood-Vessels: The aorta shows extreme sclerosis, and chronic processes are seen with atheromatous ulcers and calcified placques lying side by side. There is a diffuse dilatation of the arch and a large thrombus overlies its descending portion. The veins also show an extreme grade of sclerosis.

Microscopic Notes.

Subcutaneous Nodules: Skin nodule No. 1 removed during life (Dec. 24, 1908). The section includes the skin and subcutaneous tissues. Lying beneath the skin is a small nodule which is composed of large cavernous sinuses containing well-preserved red blood. The walls of these sinuses are, for the most part, quite thin, lined on either side by flat endothelial cells, and containing between these a pinkish staining ground substance in which an occasional spindle nucleus is to be made out. Toward the periphery of the nodule the walls become slightly thicker and more cellular, resembling fibrous tissue.

Skin nodule No. 2, removed during life (Aug. 15, 1909). This nodule was cut in serial sections to show its relation to the vessels. The sections show an overlying layer of skin which is uninvolved by the tumor mass, and lying in the subcutaneous fat is a small nodule which is quite cellular. It is composed of many spindle cells which, on tangential section, have long nuclei with pointed ends. These show an outer nuclear membrane and pale protoplasm, in which numerous darker staining chromatin granules are found. The outline of the cells is, for the most part, made out with difficulty, but where they are seen, they are found to be relatively short; their protoplasm staining pale pink with delicate prolongations. The blood spaces described in Section 1 are very much less conspicuous in this section, although the tumor is quite vascular. The walls of the spaces, however, do not correspond in any way to those described in Section 1; for they are made of spindle cells similar to those described in the body of the tumor. One sees, in studying the series, that, although numerous small vessels can be seen to enter the nodule in its course, there is no large vessel connected with the tumor at any part. At no place does the mass seem to be connected with nervous tissue. An occasional nerve is found in the subcutaneous tissue, but none of these are in contact with the tumor, nor can any be seen projecting into the mass. The nodule varies somewhat in its consistence; for the most part, it is quite firm, composed of the spindle cells, above described, but occasionally small, irregular endothelial lined cavities are to be made out.

Skin Nodules at Autopsy: In order to study the nature of these vascular spaces to a greater advantage, the brachial artery was exposed and Berlin-Blue was injected. Several nodules were removed from the injected limb and studied in serial sections. In all, about 25 nodules were examined. Suffice it to say that they are all quite vascular, and in many of them there are hæmangiomatous caverns. In the surrounding subcutaneous tissue many vessels are to be found, but only small ones seem to be in direct contact with the tumor. The larger ones show an interesting change which will be described below.

On detailed examination, the nodules are, in general, quite similar. They vary somewhat in their characteristics, and it will suffice to describe completely one in which a composite picture is found, practically including the variations.

One sees a tumor mass (Fig. 3) surrounded partially by a definite membrane which is composed apparently of muscle. The cells are long and spindle-shaped, with long, pale staining nuclei, in which a considerable chromatin network can be seen. The protoplasm of these capsule cells is pale pink and stands out in sharp contrast to the cells of the tumor which have much less protoplasm and more deeply staining nuclei. This capsule surrounds the tumor in part only. In other parts it has greatly thinned out and allows the tumor mass to project into the subcutaneous fat. The tumor varies somewhat in its consistence; while in one area it is quite cellular and only a small number of blood-vessels can be made out, in other areas it is composed of blood spaces separated from each other by thin walls lined with endothelium (Figs. 4, 5).

The spaces are irregular, gradually becoming smaller as they project into the more cellular tumor. As the spaces grow smaller, their walls become considerably thickened. The walls of the large spaces are, in places, composed of but a single layer of endothelium, or may show a double layer, one lining each adjacent cavity (Fig. 6). Between this layer of endothelial cells there is a small amount of pink, homogeneous

tissue in which an occasional slender, deep blue-staining nucleus occurs. The blood in these spaces is well preserved, normal blood. As above stated, there is a simultaneous increase in the thickness of the walls with a decrease in the size of the spaces. The walls increase by fusion and by proliferation, and lose their fibrous character and become cellular. These cells resemble in every respect those lining the cavities. In this manner the angiomatous portion of the tumor merges on all sides into the cellular mass above described.

It is to be noted, however, that some of the nodules, even small ones, are composed of cell masses without blood spaces. This was brought out very characteristically in the study of one nodule in serial section, which had an hour-glass shape. This hour-glass had for its center a thick-walled blood-vessel. From the center the wall was distended and thinned toward the poles by the tumor mass, and in places the mass protruded through into the surrounding tissue. The lumen of this vessel was filled with cells indistinguishable from the endothelial lining and similar in all respects to those making up the tumor mass (Fig. 7). The appearance of this nodule led to a detailed study of the blood-vessels.

The Blood-Vessels: There was evident a marked increase in number of the vessels throughout the connective tissue, and these vessels showed great thickening of their walls, which involved all three coats. The large vessels show several types of thickening and diminution of their lumen. The changes are most marked and varied in the intima and subintimal tissue.

From a simple oval slit-like lumen (Fig. 8), lined by one layer of cells and surrounded by a greatly increased subintimal layer, poor in nuclei, it is possible to trace by steps, a gradually increasing complexity in the form of the lumen. In some vessels the lumen is encroached upon by nodular projections which give it an irregular outline like that of the Fallopian tube. In still others, bridges of tissue extend across the lumen, dividing it into separate channels (Fig. 9). These strands may be lengthened and folded so as to give the lumen a labyrinthine appearance. The bridges are lined by a single layer of endothelium and made up of the thick subintimal coat.

The small vessels are likewise greatly increased in number, many of them showing a marked thickening of their walls. While some of these show an increase in all their coats, the changes are, for the most part, in the endothelial lining. The endothelium may be increased uniformly to several layers, or it may proliferate in a nodular manner, and project into the lumen like a polyp (Fig. 10).

In other vessels the masses of endothelium seemed to lie free in the lumen and no connection with the wall could be made out in serial sections.

In another group of vessels the endothelium forms nodal thickenings of several layers at different points on the wall. Finger-like columns of cells project into the lumen from these nodes and at times the space between the fingers is bridged by a single cell. In this way the lumen is divided into two or more parts, forming angiomata (Figs. 11, 12, 13, 14).

In still other vessels multiple caverns are formed in a different manner. Here the endothelium seems to dip into the wall, or even to push the wall before it into the surrounding tissue, as bays push in from the borders of a lake. The necks of these bays are narrow and may be closed by a mass of endothelium, when we have separate caverns in juxtaposition (Figs. 15, 16).

This is a definite new formation of blood-vessels by budding similar to that seen in granulation tissue and in the embryo.

In correlating the foregoing detailed studies, we see first, a striking generalized sclerosis of the arteries and veins, corresponding to that described in the subcutaneous vessels. This thickening may be seen in all the coats, leaving a slit-like lumen, or there may be an irregular proliferation of the intimal tissue in nodes, or strands, which divide the lumen into narrow channels, or obliterate it altogether.

Associated with this narrowing of the larger stream bed, there is a development of many small vessels. But here again many of the small vessels show marked thickening and, in some, the changes are confined to the endothelium alone.

This endothelial over-growth is expressed in different modes. The simplest type is found in a loop-like dipping of the endothelium into the surrounding tissue. The loop may then be cut off in its narrow part, leaving a separate cavity.

Again, nodal proliferation may take place at several points, on the wall and these nodes may be prolonged to form bridges dividing the vessel into different compartments.

Lastly, the nodal proliferation may fill the vessel with a solid mass of cells and even invade the surrounding tissue.

In this way we trace the formation of cavernous angiomata and of solid tumors to the same basal process, namely, the vegetative overgrowth of endothelium. In comparing the larger nodules of the subcutaneous tissue, we find a close relation to the changes described in the small vessels, some of these nodules showing cavernous structures in which the endothelium has obliterated the cavities in varying degrees; and in others, solid masses of endothelial cells without any trace of a preceding angioma. The question arises whether these nodules are all primary or in part metastatic. From the observations above described—that isolated masses of endothelial cells occur in some of the smaller vessels, and that no root or connection with the neighboring wall could be found in serial section, it seems probable that metastases play some part in the multiple tumor formation.

Intestinal Nodules: These all arise in the submucosa. They vary considerably in size; the smaller ones do not invade either the mucosa or the muscularis, but as they grow larger these structures are gradually involved. The tumor mass in some places pushes the mucosa outward and is separated from it by the muscularis. In other areas this line of demarcation is not apparent (Fig. 17), and one sees the tumor invading directly the villi. Such villi no longer show their normal structure; they are dilated and club-shaped, entirely denuded of their surface epithelium, and show only an occasional small atrophic gland in their bodies. The villus, except where it is replaced by tumor cells, is composed of dilated blood-vessels

and areas of round cell infiltration. As the tumor invades the muscular coat it follows the course of the vessels in finger-like projections which gradually obliterate the muscle bundles (Fig. 18).

The nodules vary considerably in structure. Some are quite solid, others contain numbers of well-formed blood-vessels (Fig. 19), and others again show large irregular cavities lined with endothelium (Fig. 20). These cavities do not contain blood, but only precipitated albuminous material. The nature of the above cavities is best shown in the portion of intestine injected at autopsy. This part of the gut was first injected through the mesenteric artery with carmin-gelatin, and then the lymphatics of the same piece were injected with India ink. The India ink injection was not altogether successful, but did enter some of the nodules.

On serial section of the injected nodules, their general charactertistics are as described above. The carmin-gelatin has filled all the blood-vessels in the several intestinal coats and in the tumor nodules. Even the finest capillaries are injected. It becomes apparent at once that many of the large vessels and spaces with endothelial lining contain neither blood nor injection mass, but only the albuminous material previously noted (Fig. 20). These cavities lie within the tumor nodules and resemble exactly those described in the subcutaneous tissue, except that they do not contain blood. The cavities are divided into compartments by strands of tissue, varying in thickness. The thinner strands consist of two layers of endothelial cells with a very slight fibrous tissue between. In the thicker ones the walls are made up of numerous layers of endothelial cells similar to those lining the cavities. The endothelial cells are spindle-shaped, with long blue-staining nuclei and scanty pink protoplasm. Here and there the nuclei are more vesicular or show mitoses.

Selecting a node which has been injected with India ink, as well as carmin, we find that the cavernous spaces are filled with the black mass (Fig. 21), and on tracing this through a series of sections, it is found that one of the large injected lymph vessels of the submucosa opens directly into the cavity. It is, therefore, certain that the angiomàta of the intestine arise from the lymphatic vessels. That they are not hæmangiomata is evident from the fact that they do not contain any of the carmin-gelatin, which fills all the blood-vessels, but only the India ink, which is confined to the lymphatic channels.

The cavernous areas merge on all sides into solid tumors, just as the areas described in the hæmangiomata from the subcutaneous tissue.

Scattered through the more solid parts of the nodules are narrow channels lined by endothelium. These do not contain blood or carmin-gelatin and are evidently not blood-vessels. On tracing them through serial sections, they gradually increase in size and merge into cavernous spaces, or into large lymphatic vessels (Fig. 22). These latter show large projections into the lumen from either wall, which are apparently valves. These lymphatic channels are especially numerous about the larger blood-vessels which intersect the tumor nodules.

The blood-vessels themselves show a general thickening of their walls. Here and there the endothelium of the lymphatic channels is proliferated to form nodes on the vessel wall, projecting into the lymph spaces. The cells in the nodes have the characteristic perithelial arrangement, with the strands of cells at right angles to the axis of the vessel (Fig. 23). In many instances this nodular growth completely surrounds the blood-vessel.

In résumé, then, we find that the endothelium of the intestinal lymphatics has proliferated at many points to form nodular tumors. In these tumors many of the lymphatic vessels are obliterated by the endothelial masses. Other vessels are dilated, and here and there the proliferation has resulted in definite cavernous angiomata.[1]

The structural similarity of the subcutaneous and intestinal tumors suggests a possible analogy in their mode of formation. In the subcutaneous tissue there is a marked obliteration of the larger blood-vessels (generalized sclerosis) and an active production of new blood-vessels has taken place. In these small vessels the endothelium shows marked proliferative growth leading to the formation of angiomatous caverns and to solid endothelial tumors. Similarly, from some cause unknown, there has been an active proliferation of the endothelium in the intestinal lymphatics, leading, again, to the production of cavernous angiomata and solid endothelial tumors.

Stomach.

A. Mucosa in General: The gastric mucosa (Fig. 24) is thinner than normal and is everywhere covered by an exudate composed of mucus, red blood cells, and desquamated epithelial cells. The mucosa presents a picture of diffuse chronic gastritis with increase of fibrous tissue and round cell infiltration. In many places the villi are denuded of epithelium, but, as the submucosa is approached, the glandular structures become more prominent and show many changes. Some glands are atrophic, with degenerated epithelium. Others are hypertrophied and show as tortuous crypts or as groups of normal gland tissue in cross-section.

The glands may become greatly dilated at their bases and be lined either by columnar mucous cells or by a flat epithelium.

B. Polypi: These are so numerous and show such complex changes that we shall only describe the types of variation observed.

The simplest polypi are sessile and show a mass of acini separated by a small amount of fibrous tissue (Fig. 25). Many of the acini are slightly tortuous and all are lined by normal goblet cells (Fig. 26).

All the other types of polypi show not only glandular hypertrophy, but also chronic inflammatory changes. In some of them the inflammatory change predominates and there are

[1] Tumors of similar structure were found in the œsophagus, stomach, mesentery, and adrenal capsule, as well as in the intestines.

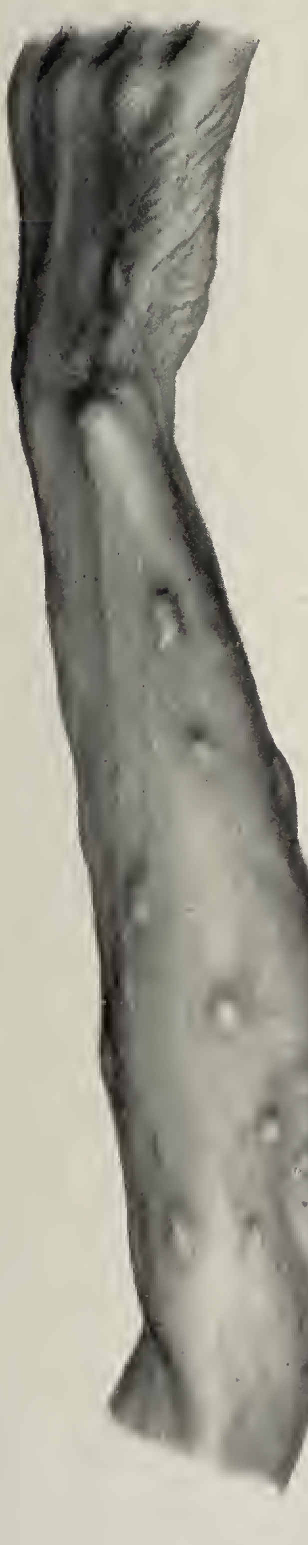

Fig. 1.—Drawing of right fore-arm showing subcutaneous nodules.

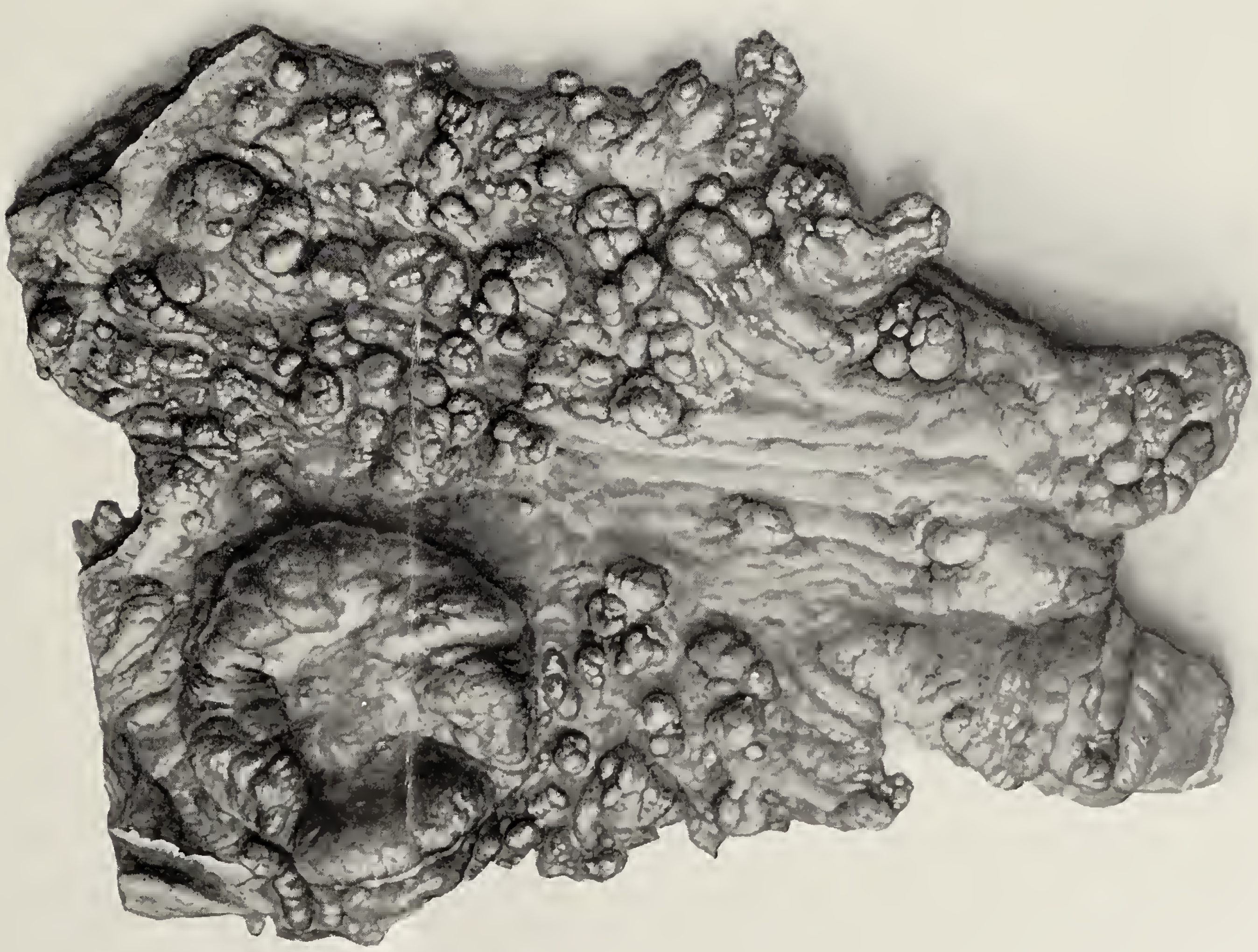

Fig. 2.—Photograph of stomach opened along the greater curvature.

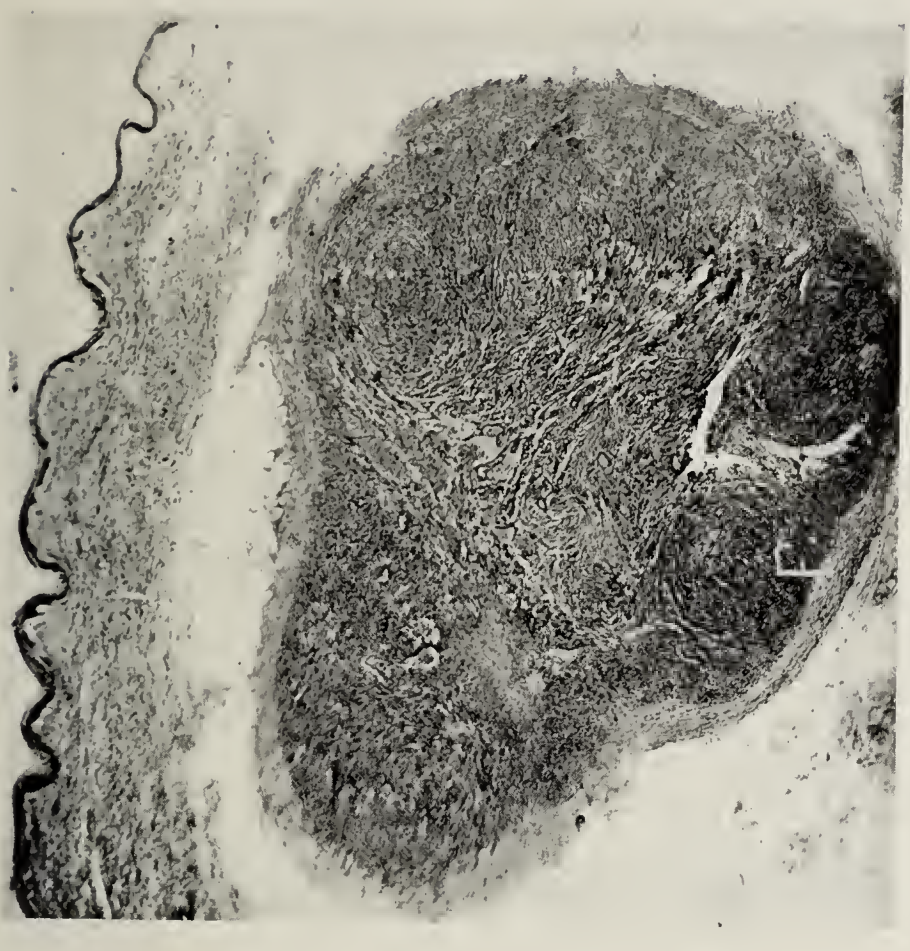

Fig. 3.—Subcutaneous nodule of mixed type with angiomatous and solid portions.

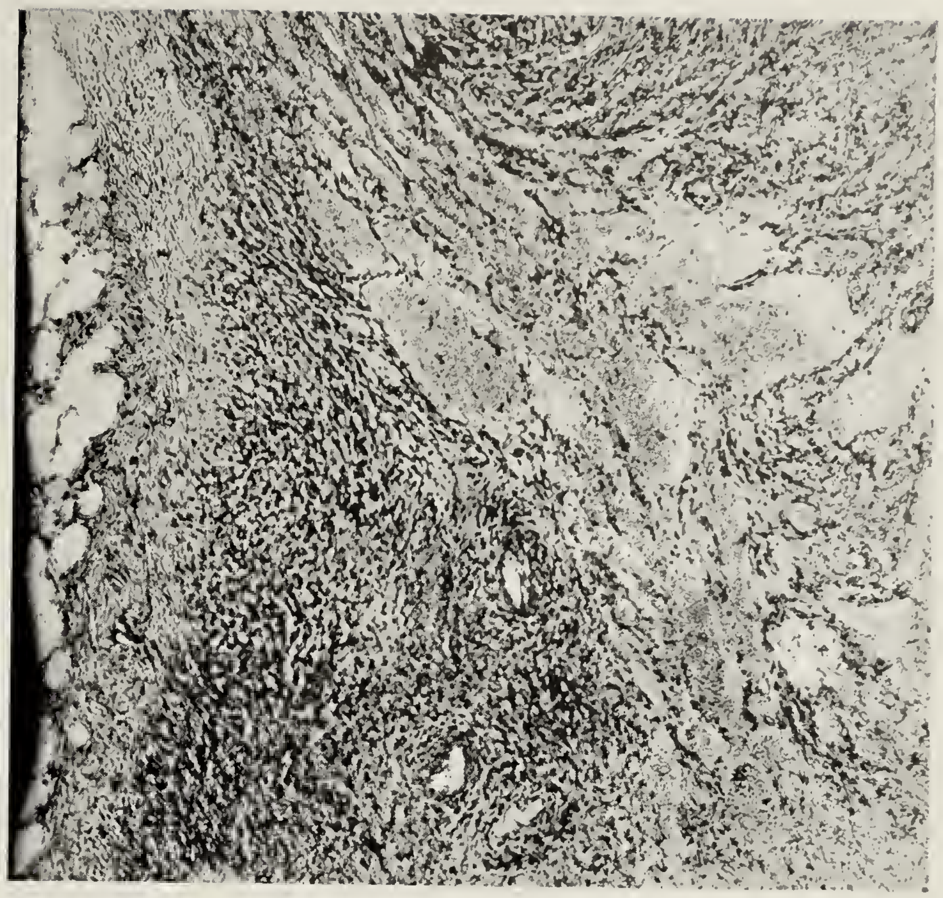

Fig. 4.—Same as Fig. 3. Higher magnification showing capsule and blood spaces.

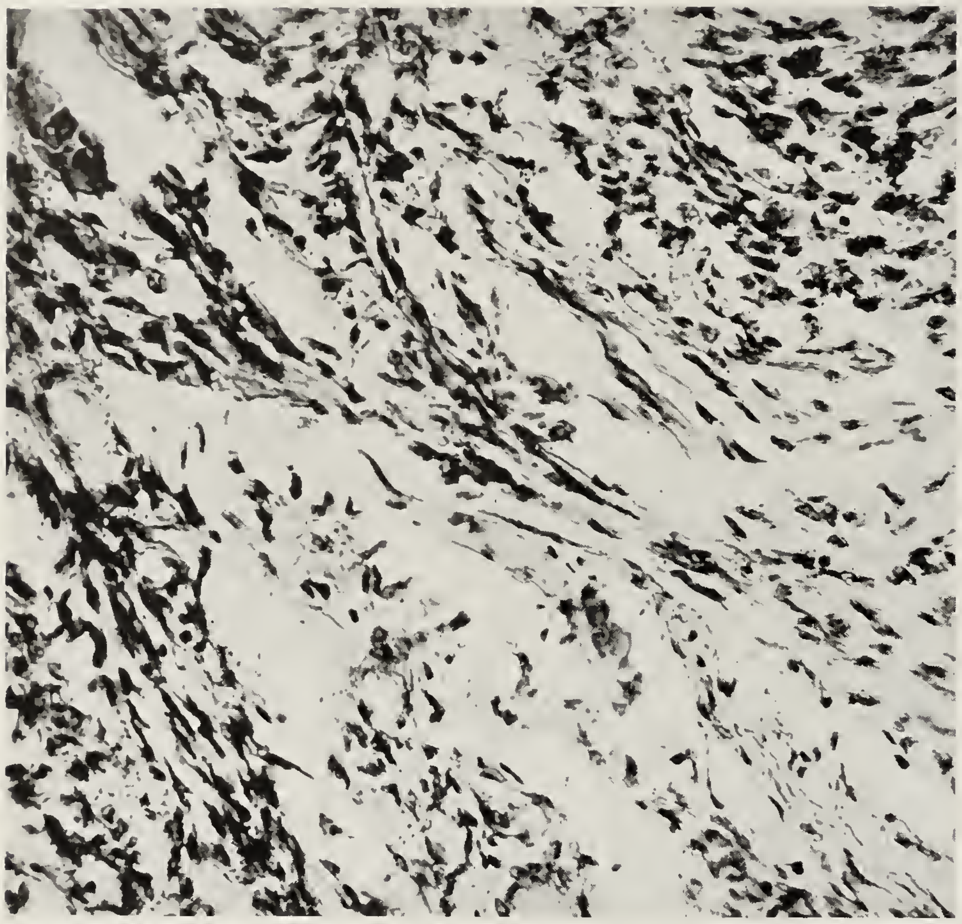

FIG. 5.—Same as Fig. 3. Higher magnification showing character of endothelial cells.

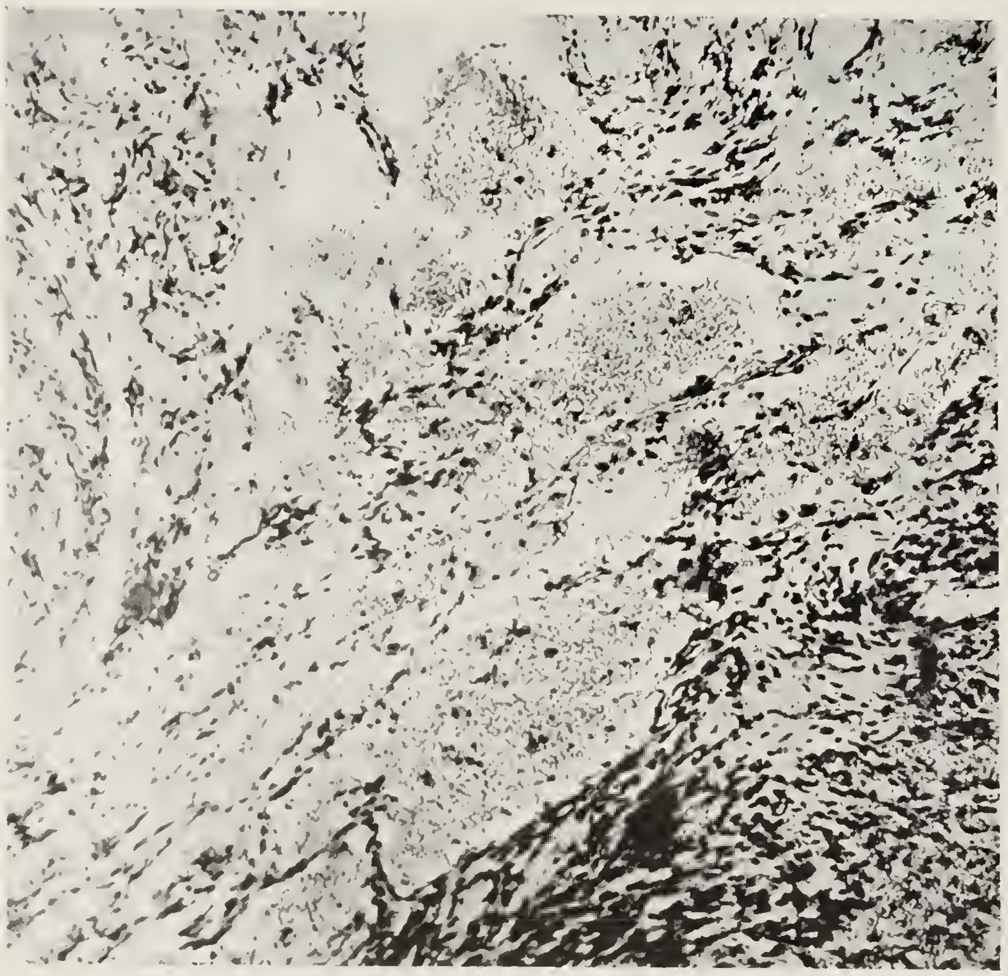

FIG. 6.—Same as Fig. 3. Higher magnification showing character of angiomatous portion.

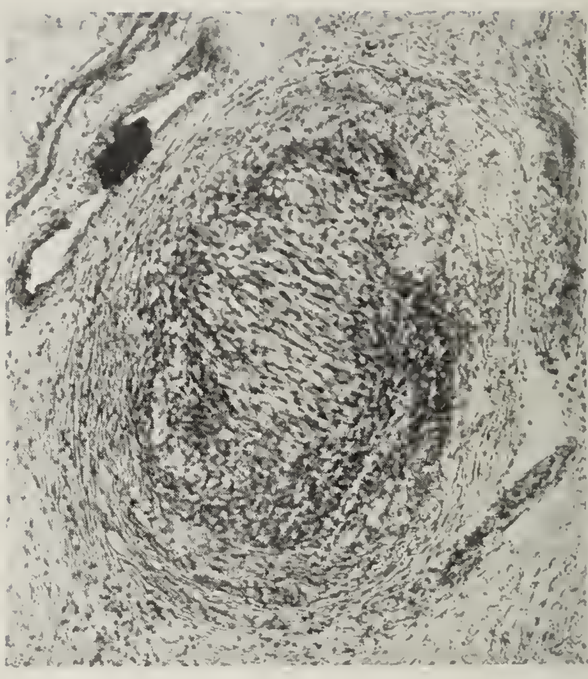

FIG. 7.—Center of hour-glass nodule. The lumen of the vessel is completely filled with endothelial cells.

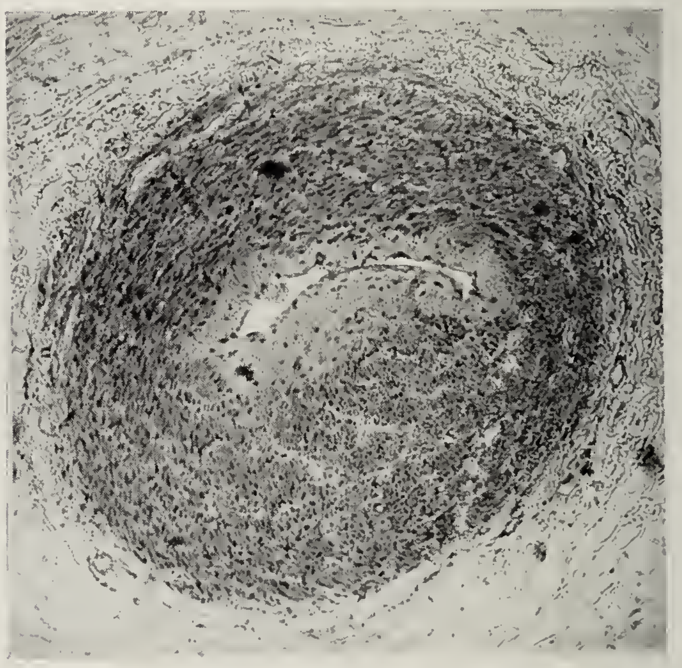

FIG. 8.—Sclerotic subcutaneous vessel showing slit-like lumen.

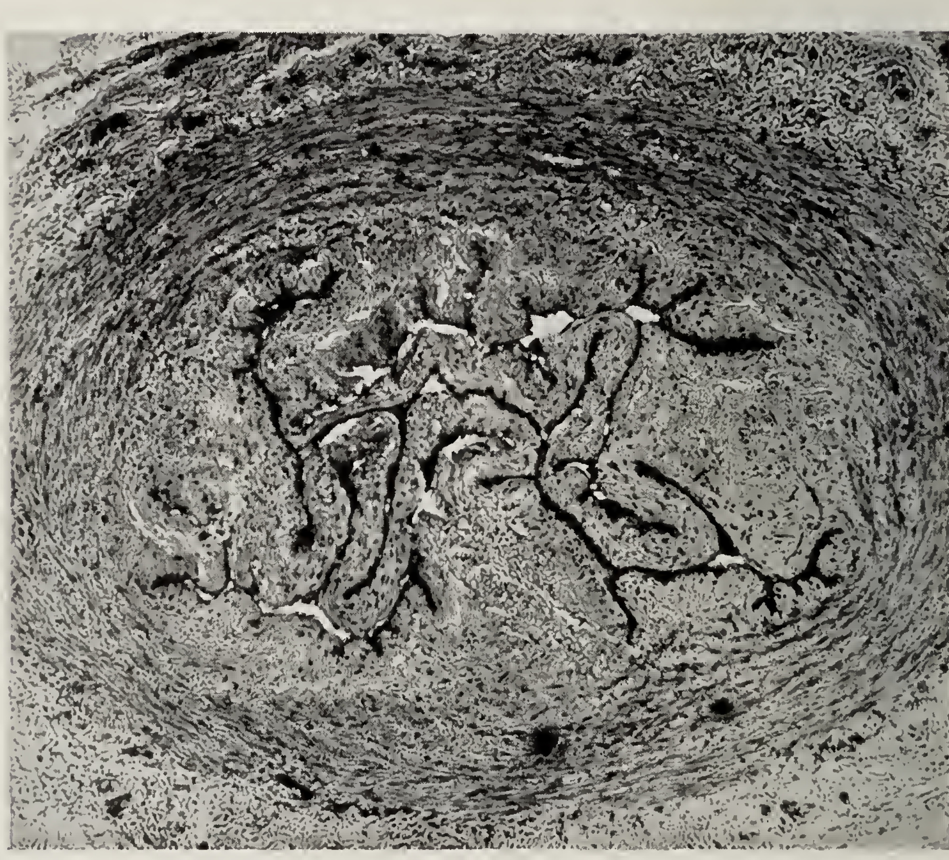

FIG. 9.—Another vessel showing extreme proliferation of intimal and subintimal coats with labyrinthine lumen.

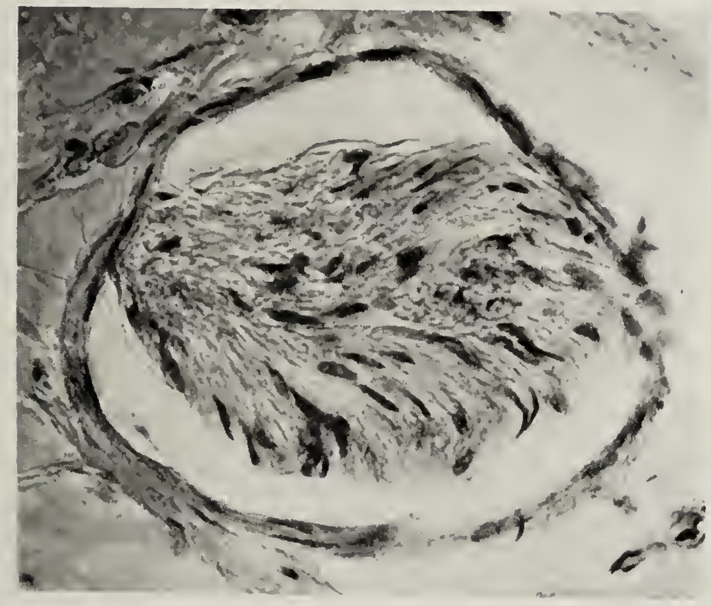

Fig. 10.—Polypus-like outgrowth of endothelial lining of a small vessel.

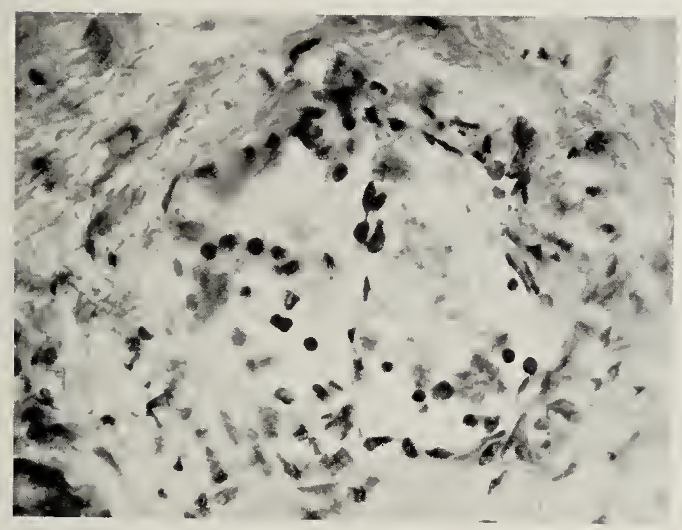

Fig. 11.—Outgrowth of endothelial strands in small vessel forming separate channels.

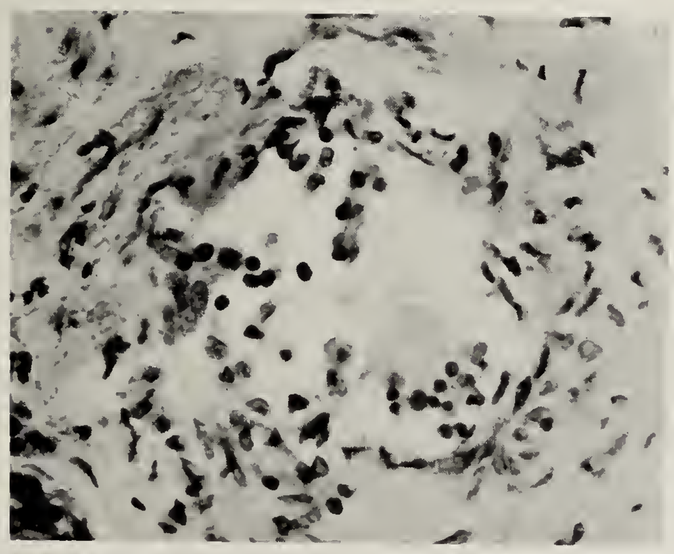

Fig. 12.—Same as Fig. 11. Slightly different focus.

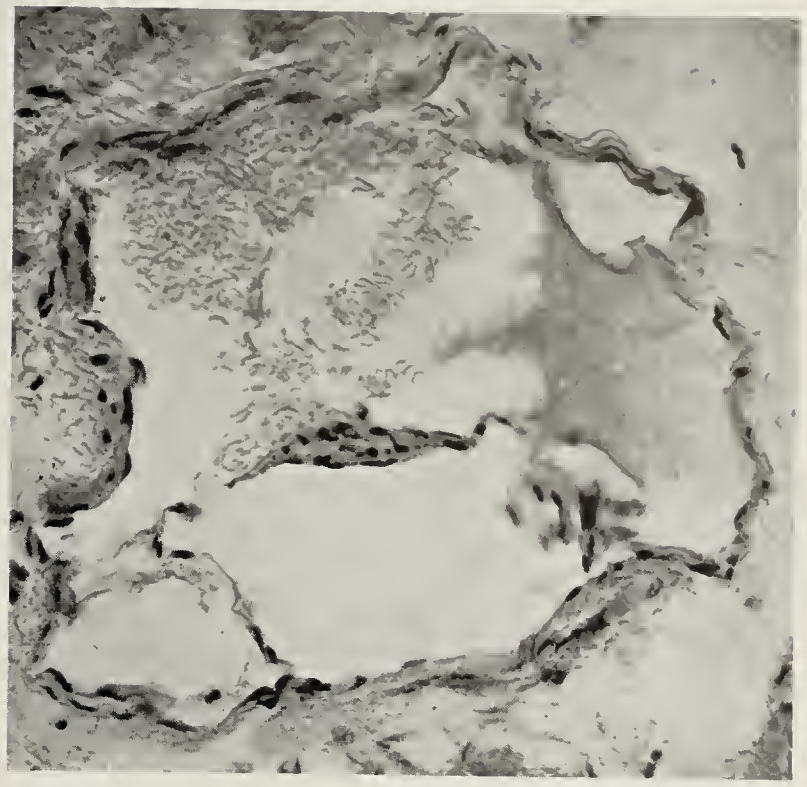

Fig. 13.—Subdivision of larger vessel by strands of endothelium.

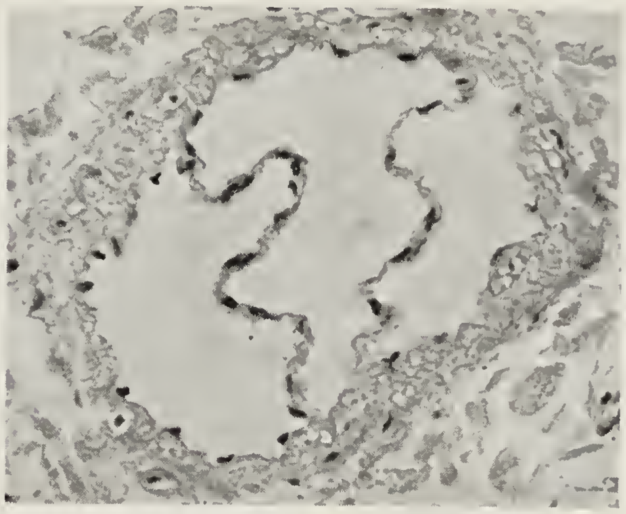

Fig. 14.—Valve-like strands in small vessels.

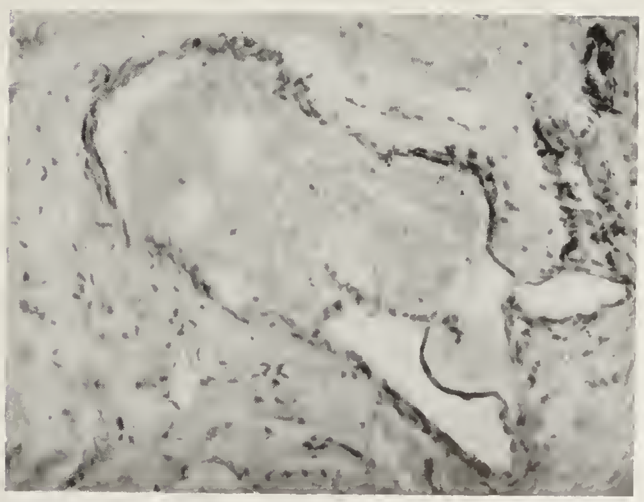

Fig. 15.—Formation of separate channels by budding.

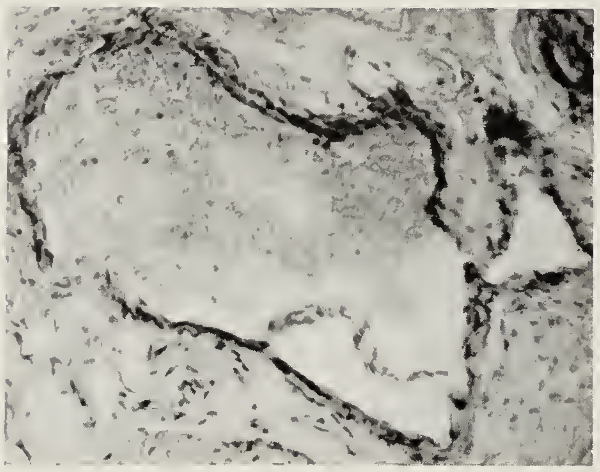

FIG. 16.—Same as Fig. 15.

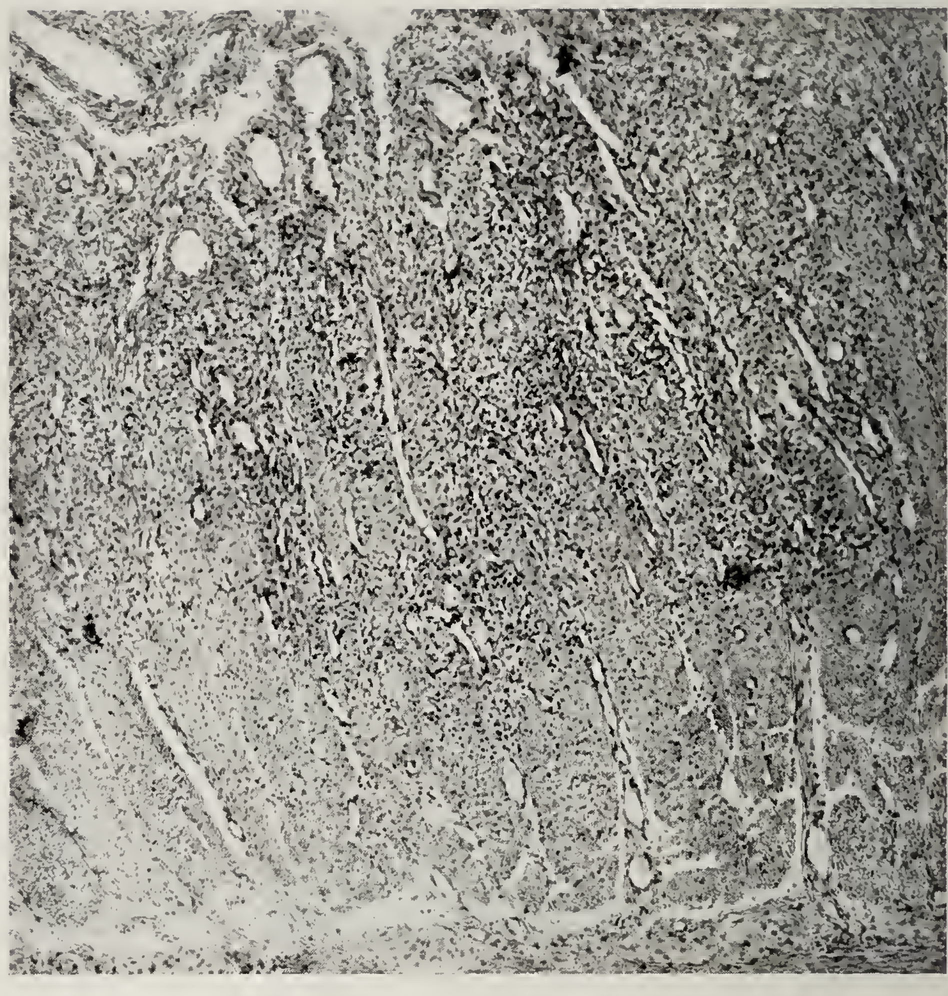

FIG. 18.—Intestinal nodule invading muscularis.

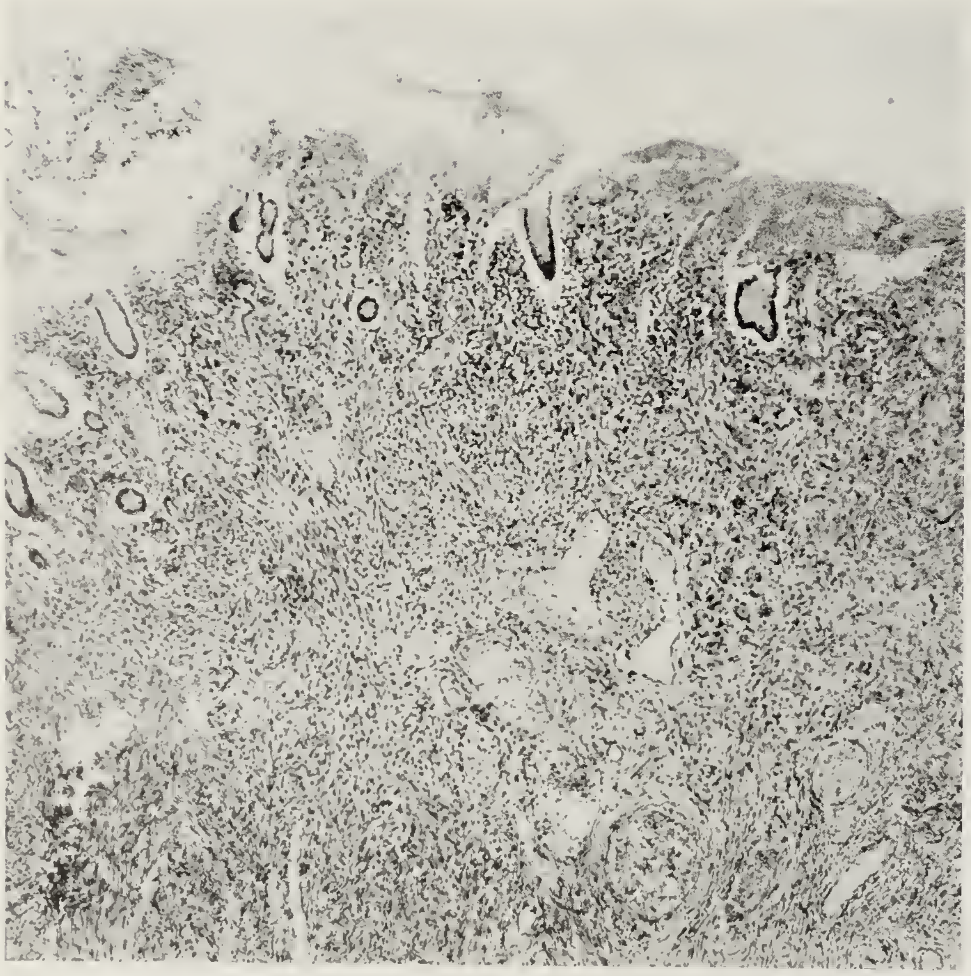

FIG. 17.—Intestinal nodule invading villi.

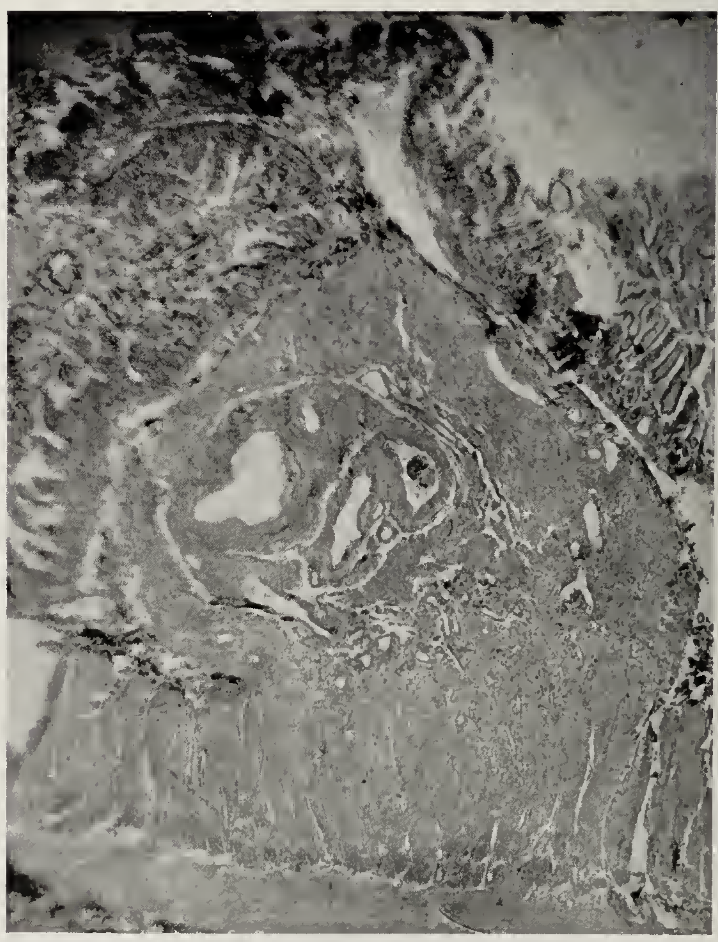

FIG. 19.—Intestinal nodule showing larger blood-vessels.

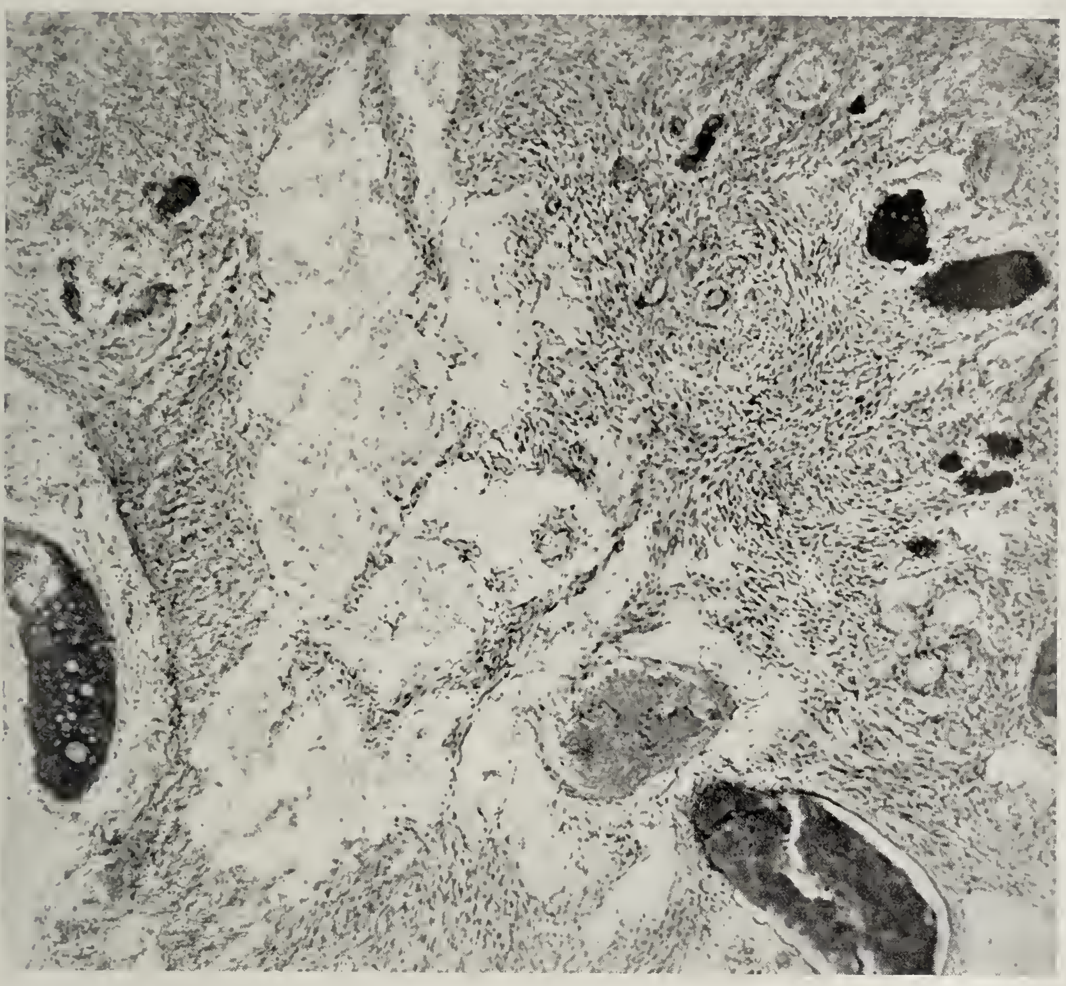

Fig. 20.—Intestinal nodule showing lymphangiomatous caverns.

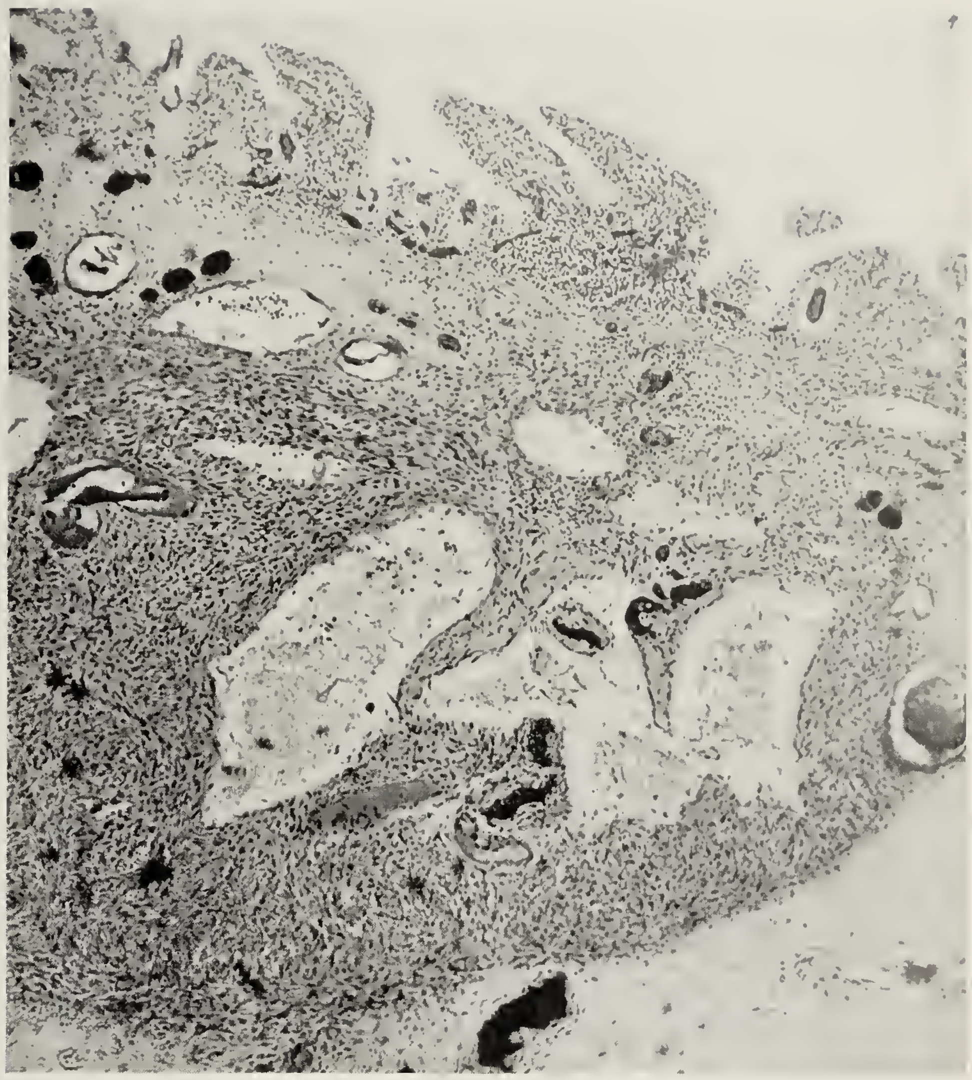

Fig. 22.—Intestinal nodule showing dilated lymphatics with valves.

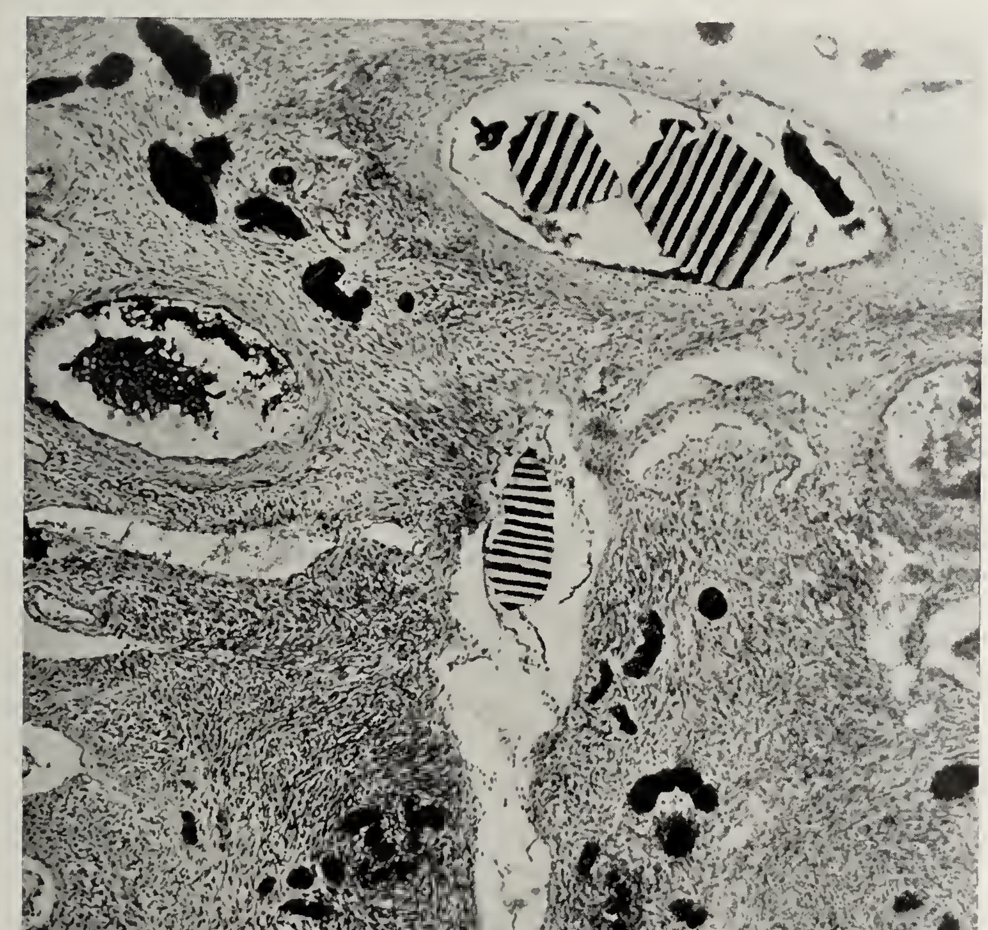

Fig. 21.—Intestinal nodule injected with India ink. White lines crossing the black show injection mass. Dark masses without lines show carmin-gelatin in the blood-vessels.

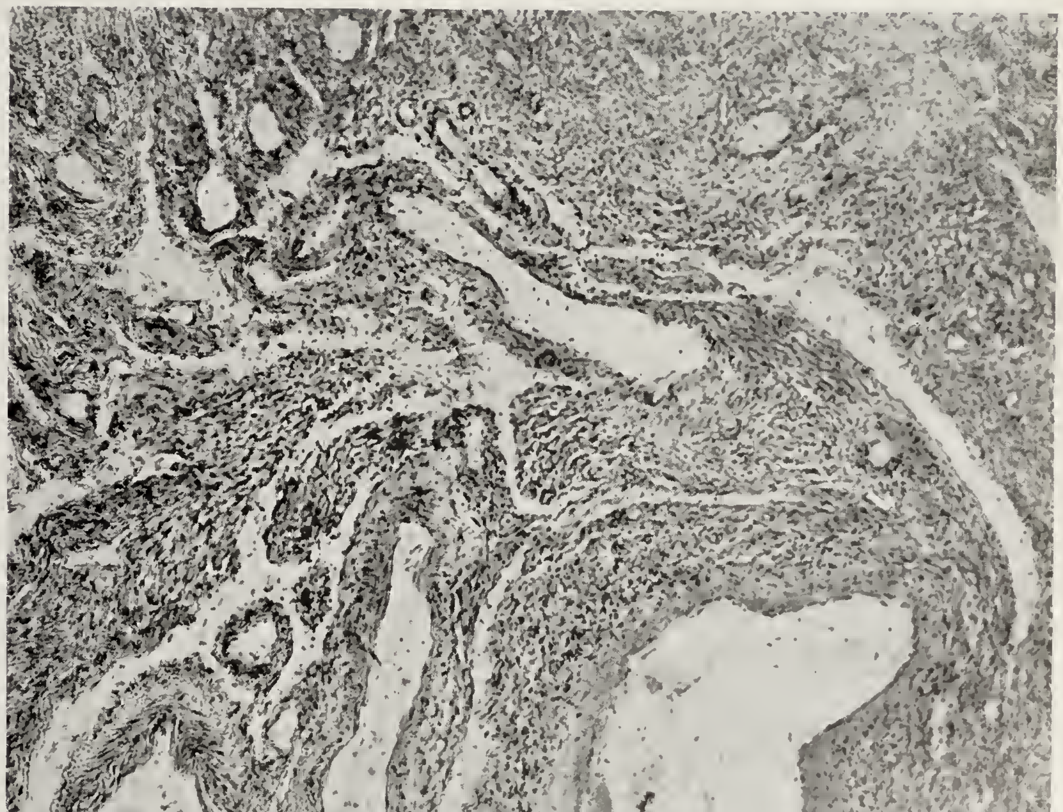

Fig. 23.—Same as Fig. 19. Higher magnification showing endothelial proliferation in the lymph spaces.

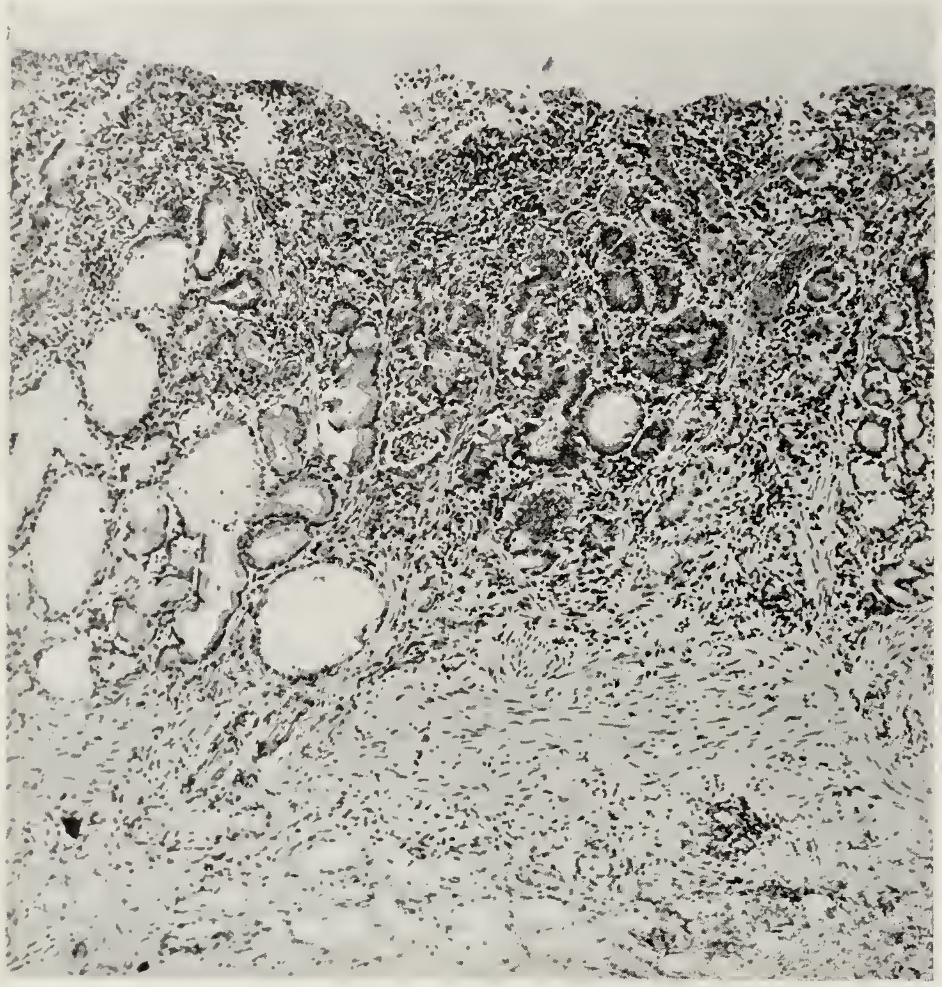

FIG. 24.—Chronic gastritis.

FIG. 26.—Same as Fig. 25. Higher magnification.

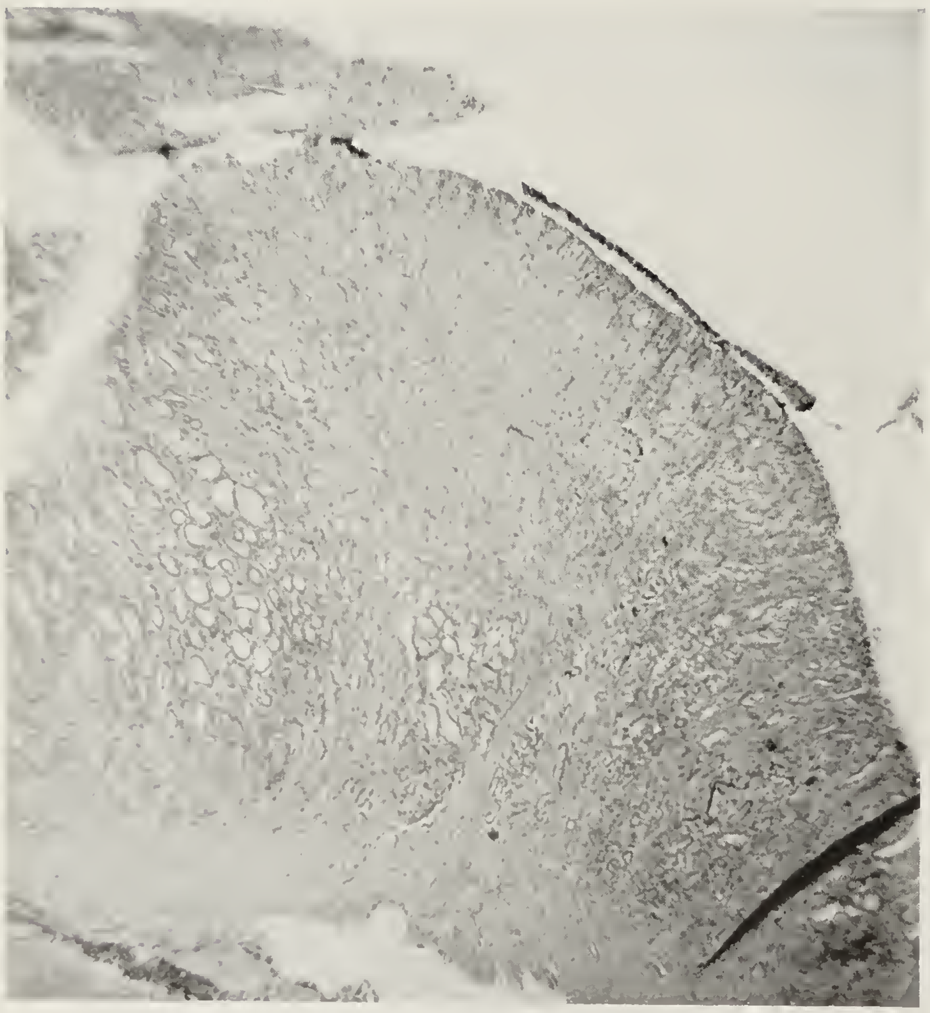

FIG. 25.—Sessile polypus.

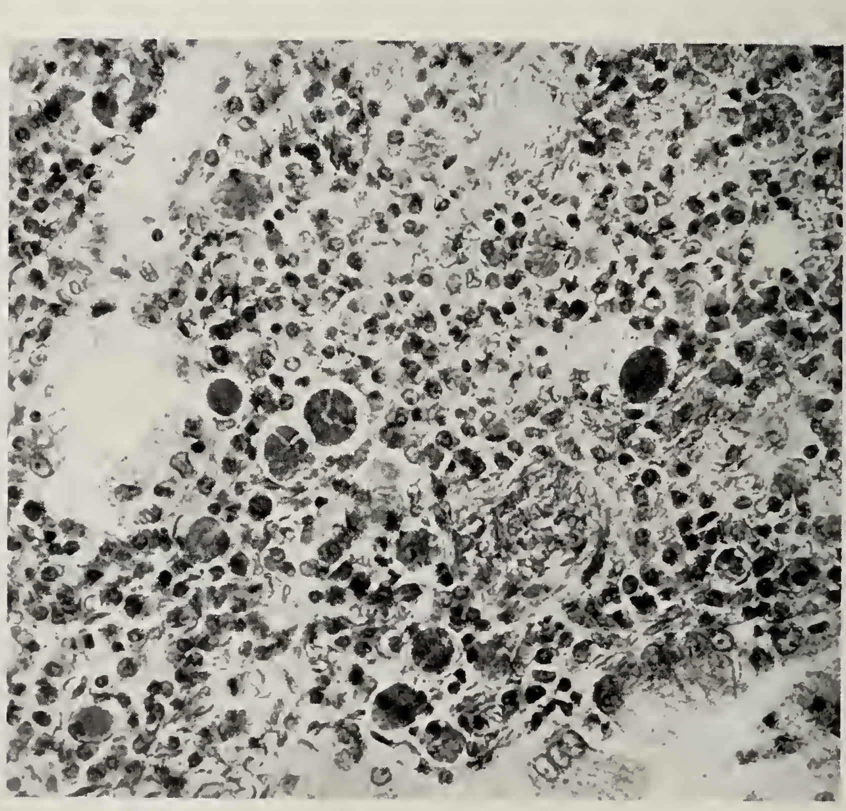

FIG. 27.—Chronic gastritis showing "Russell's Bodies."

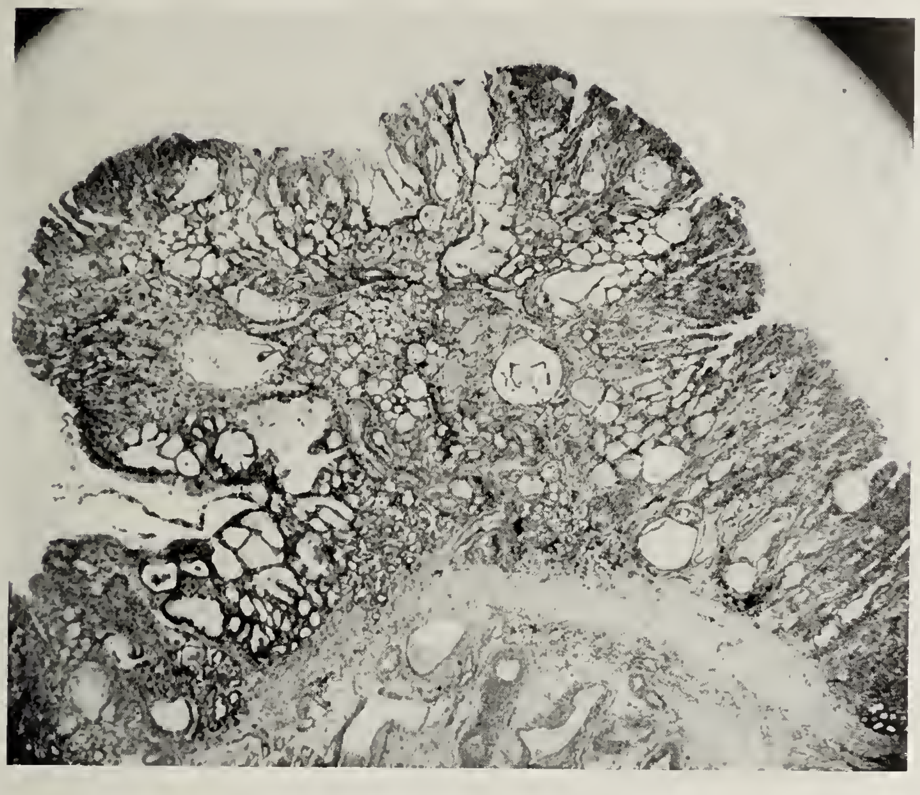

Fig. 28.—Cauliflower polypus.

Fig. 29.—Cauliflower polypus.

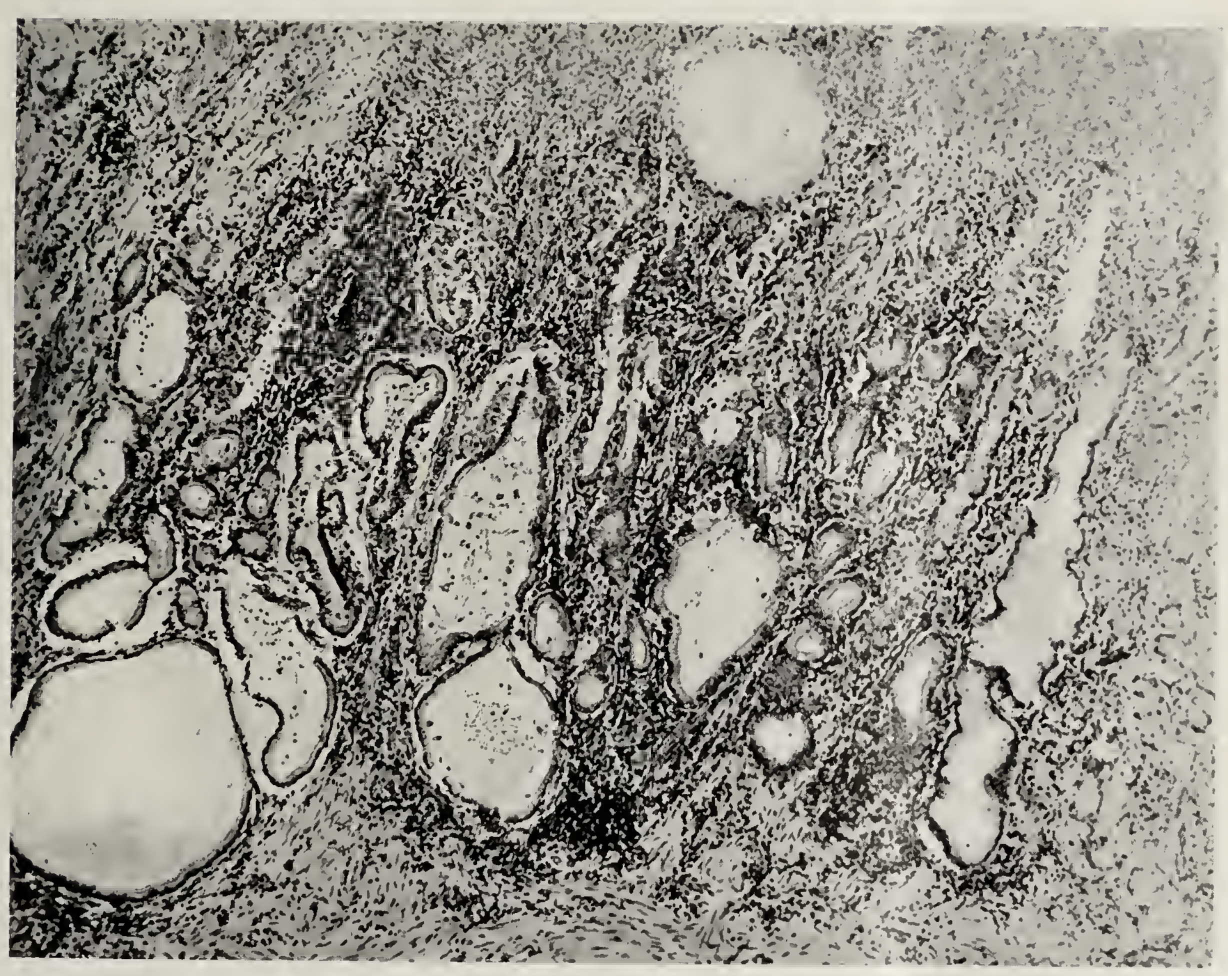

Fig. 30.—Same as Fig. 28. High magnification showing tortuous and dilated acini.

Fig. 31.—Same as Fig. 29. Higher magnification of acinus, showing papillomatous proliferation of epithelium.

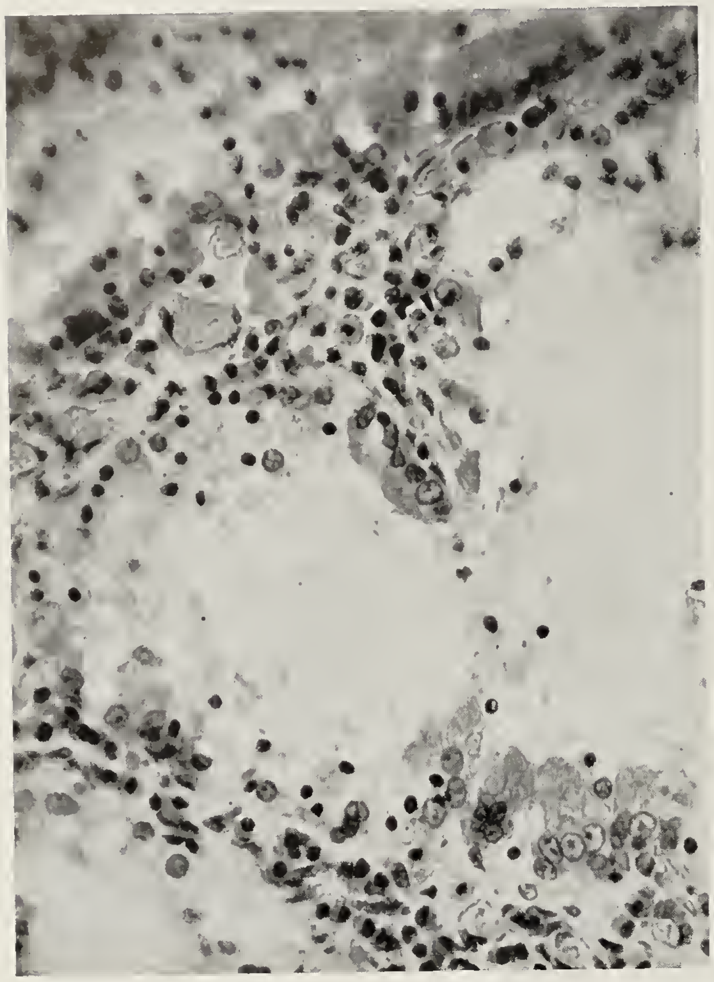

Fig. 32.—Same as Fig. 31. Higher magnification showing atypical epithelial cells.

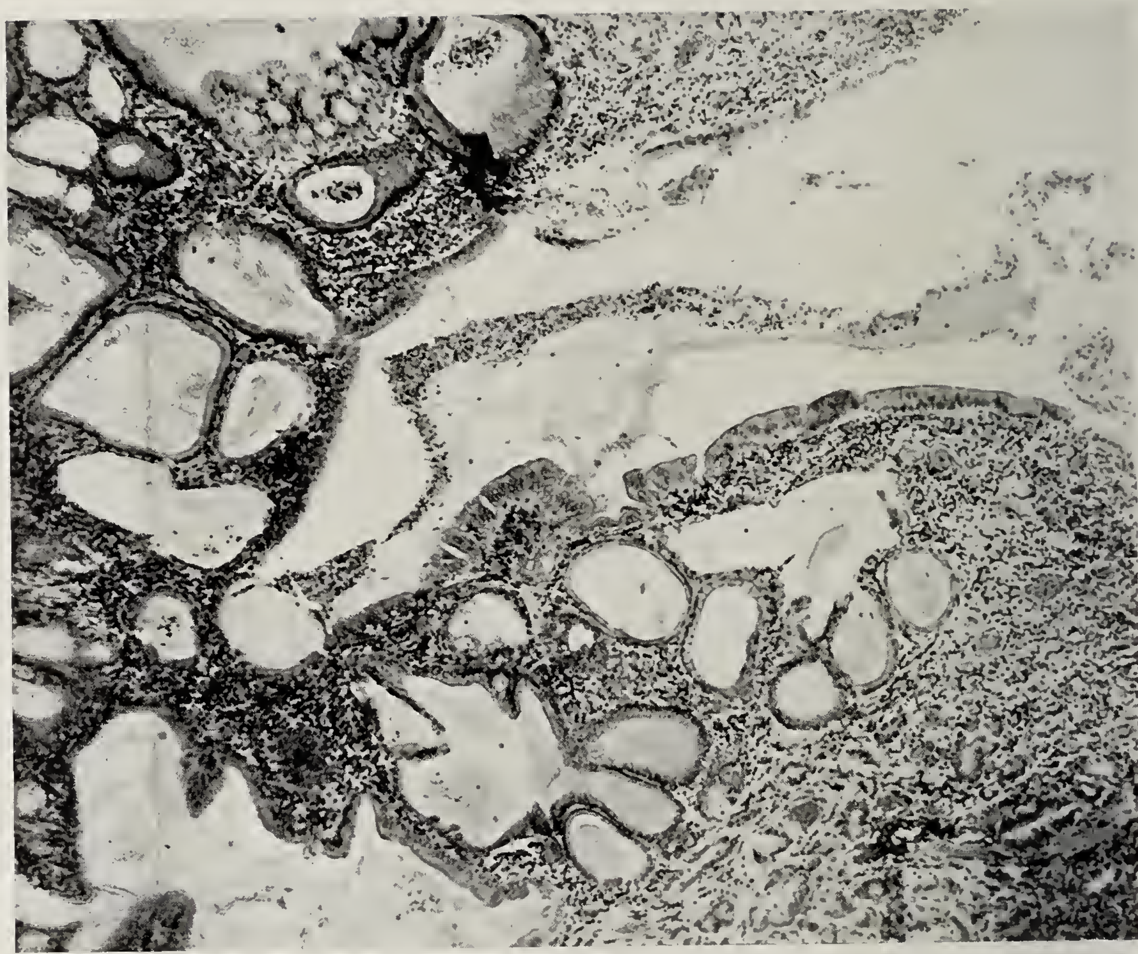

Fig. 33.—Crypt from Fig. 28.

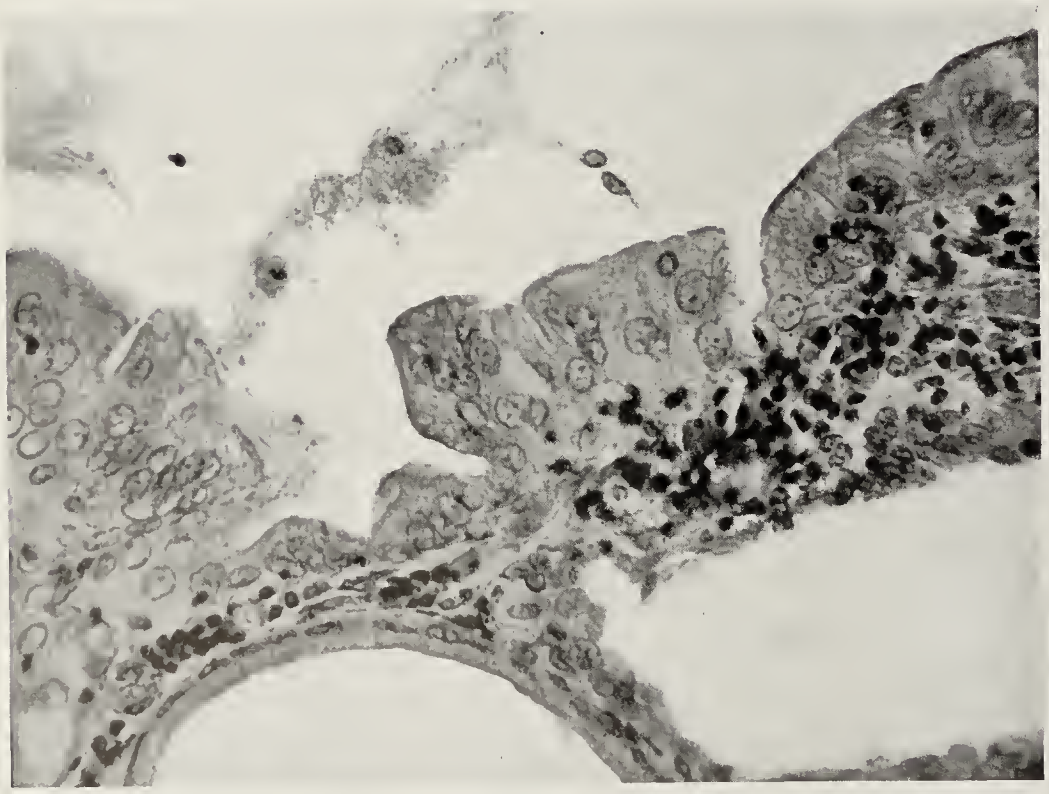

Fig. 34.—Same as Fig. 33. Higher magnification showing proliferation of epithelium and multinuclear cells.

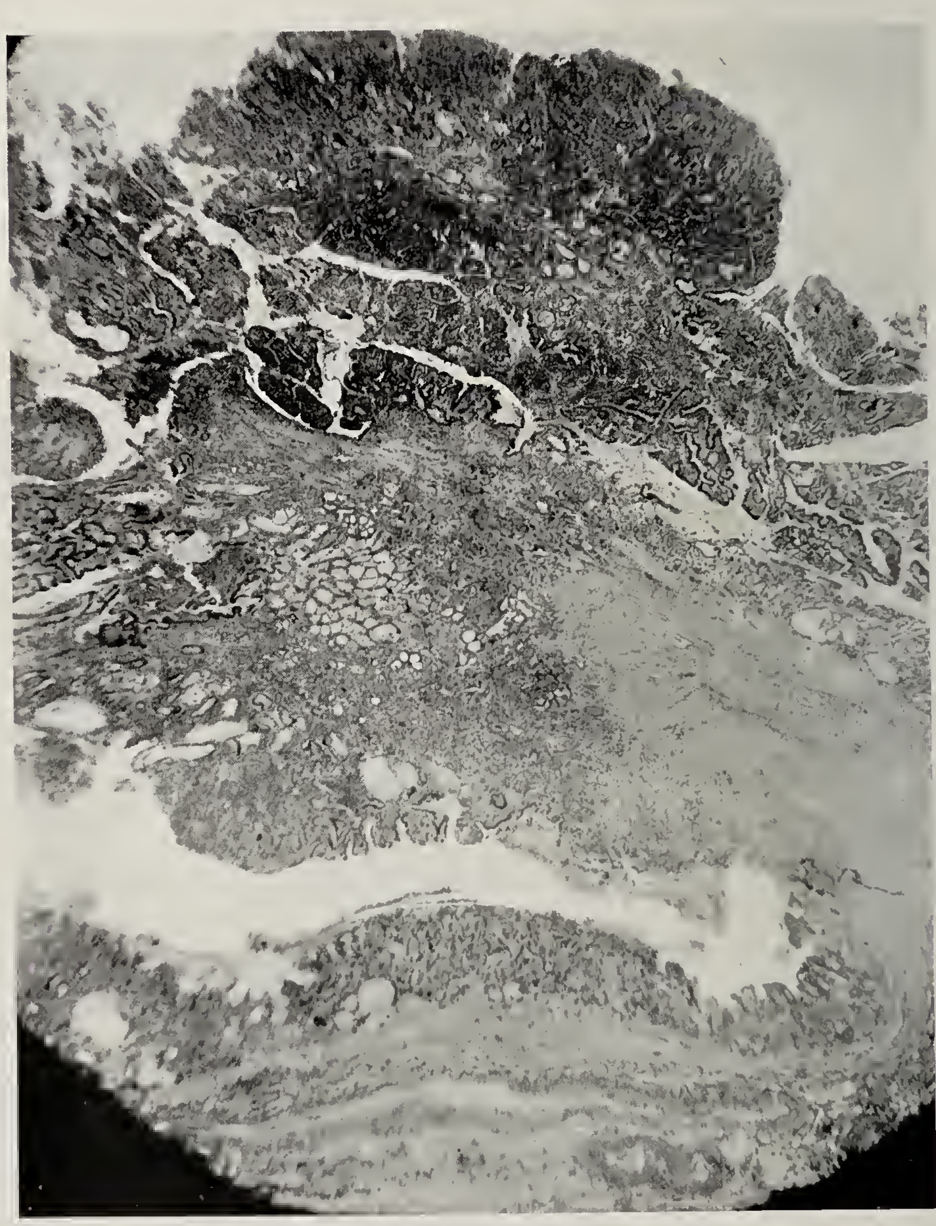

Fig. 35.—Cauliflower polypus showing adenomatous change.

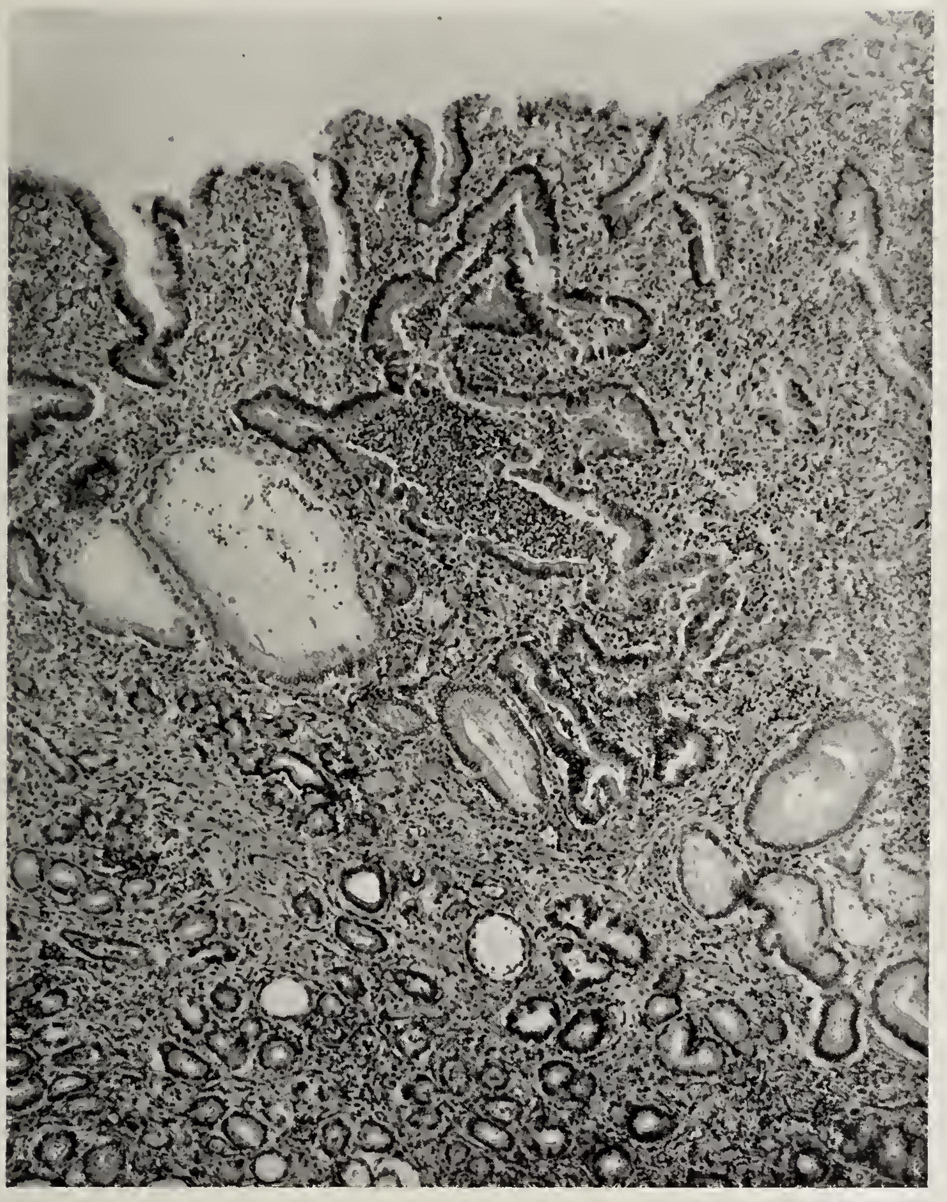

FIG. 36.—Same as Fig. 35. Higher magnification.

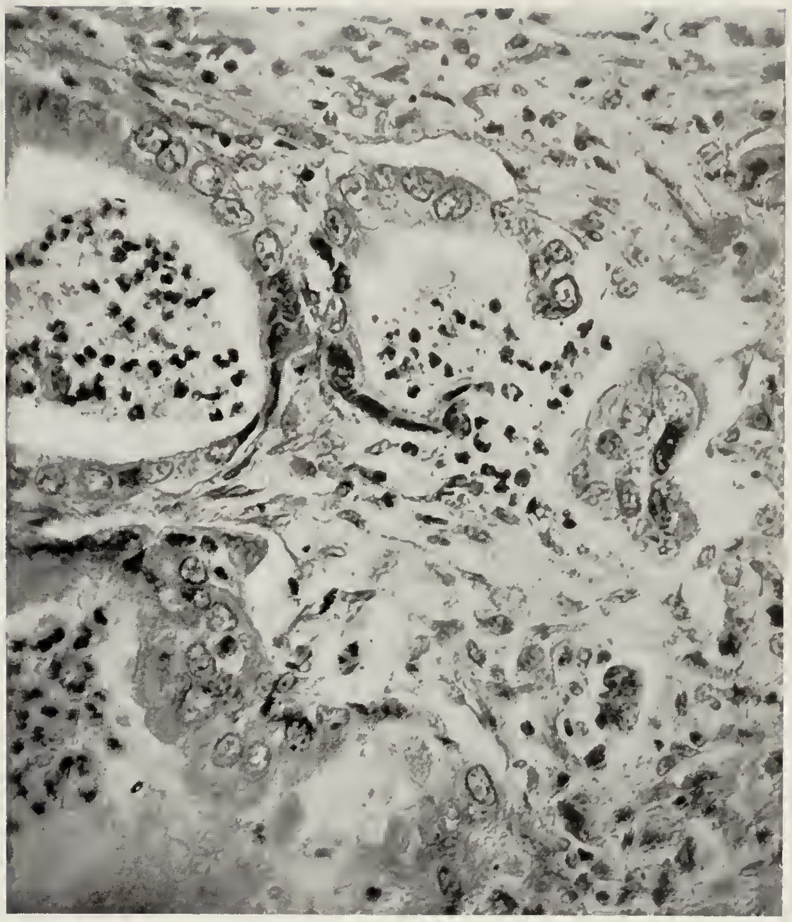

FIG. 38.—Acinar epithelium invading basement membrane.

FIG. 37.—Portion of adenomatous polypus showing normal and undifferentiated acinar epithelium.

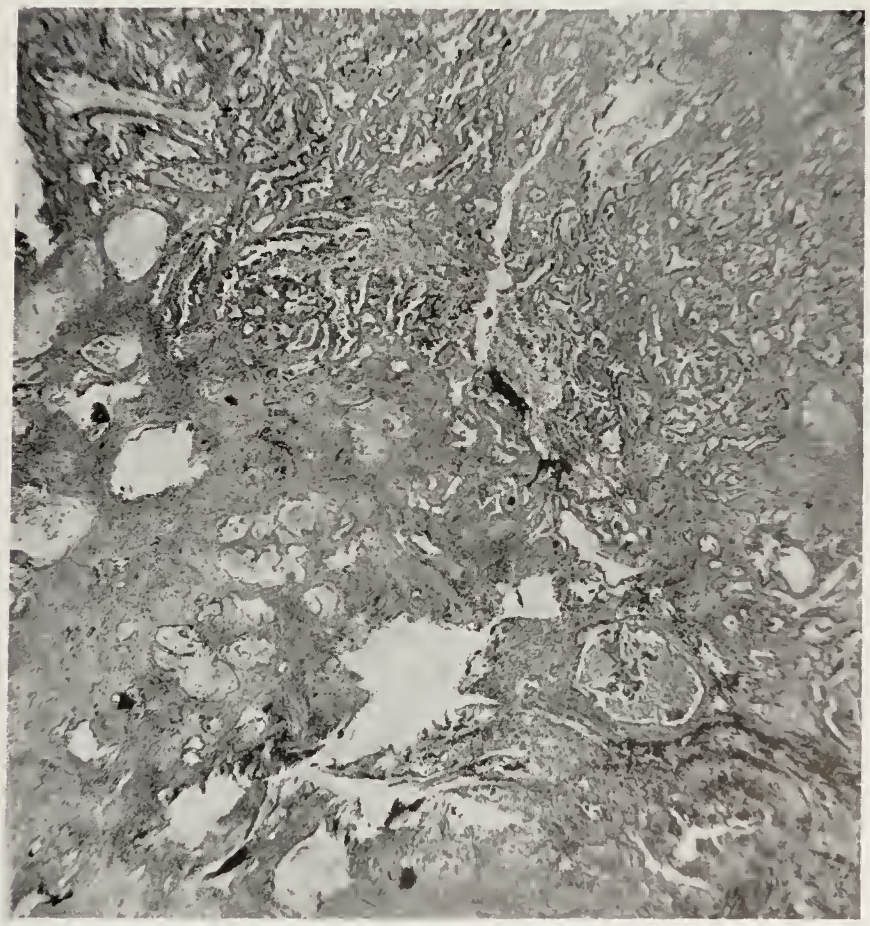

FIG. 39.—Cancerous polypus invading muscularis.

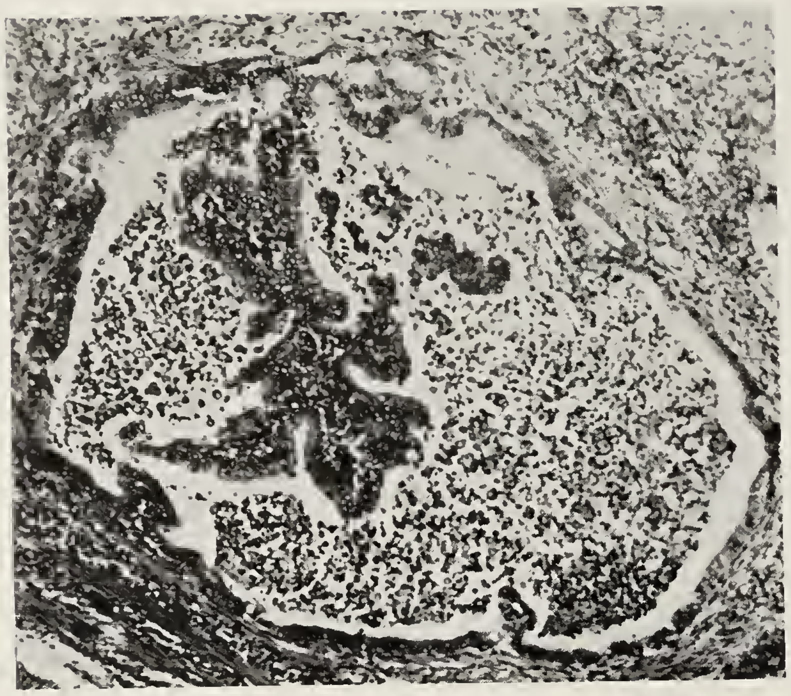

Fig. 40.—Same as Fig. 39. Higher magnification of acinus.

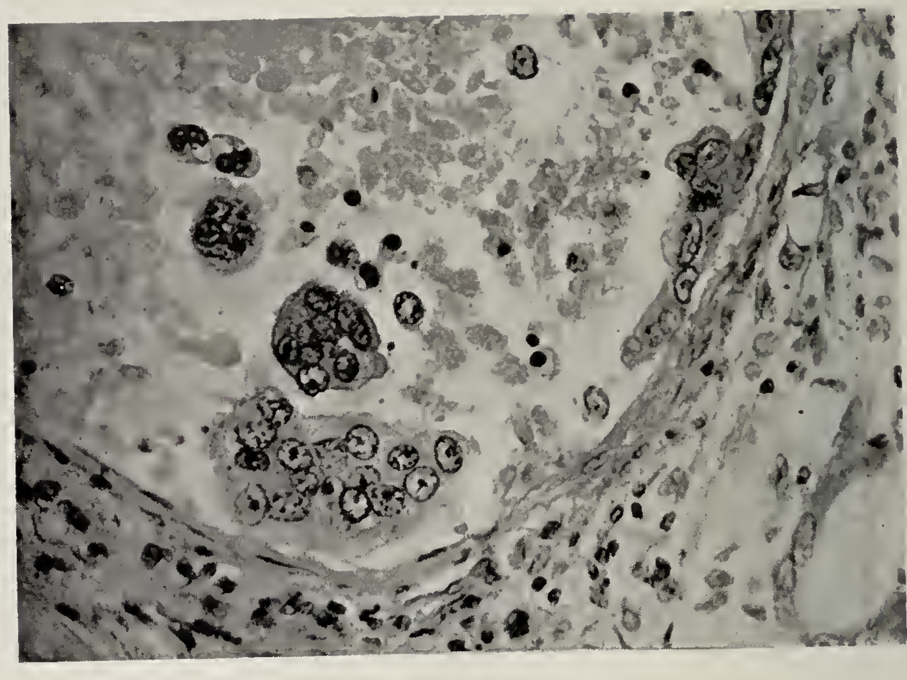

Fig. 42.—Same as Fig. 41.

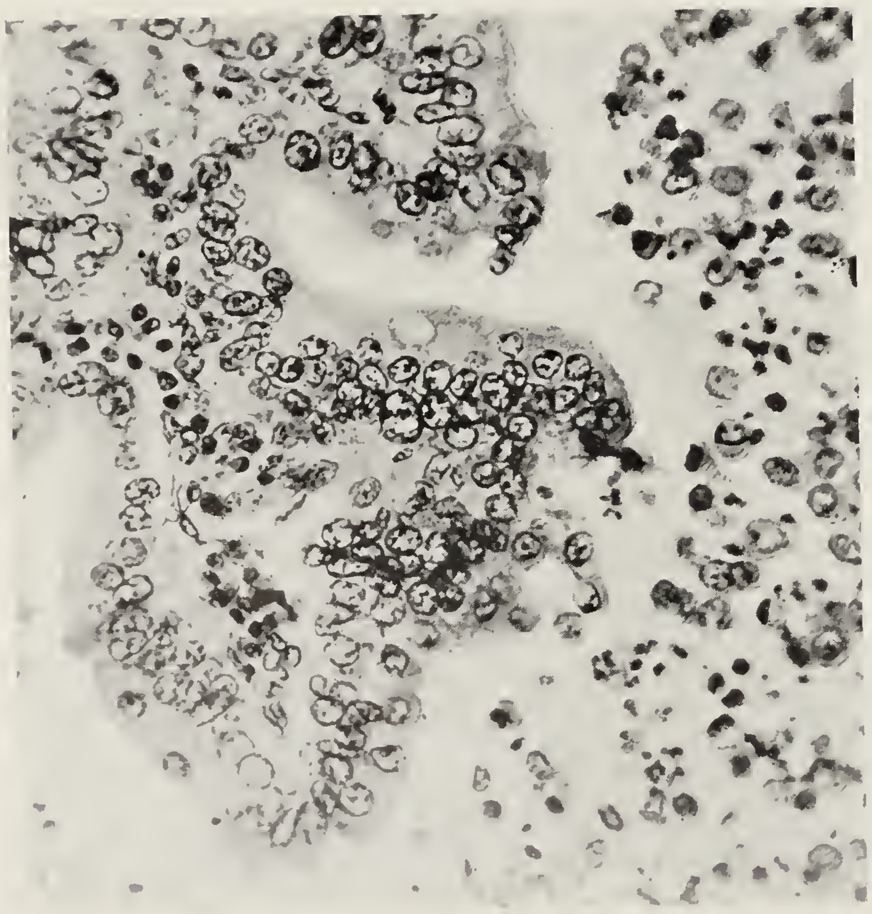

Fig. 41.—Same as Fig. 40. Higher magnification showing cancerous character of epithelium.

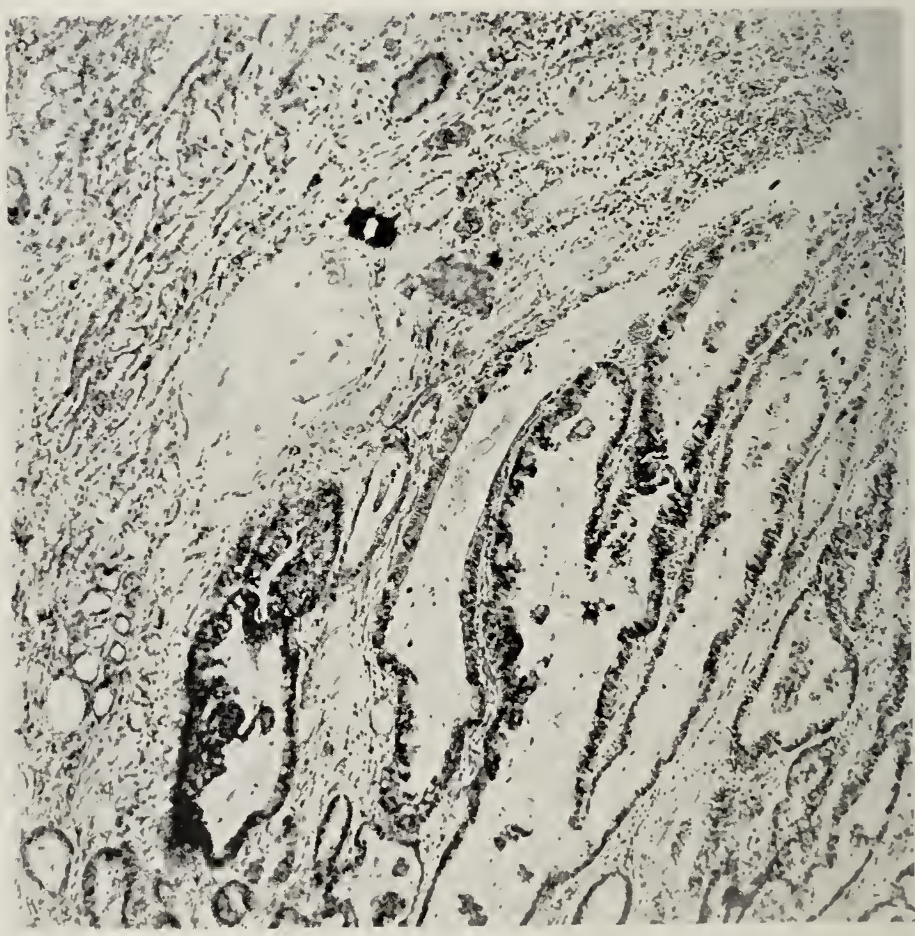

Fig. 43.—Cancerous metamorphosis of mucosa uninvolved by polypus.

large areas where no acini are found, but only masses of fibrous tissue with round cell infiltration. Many cells in these areas show a hyaline, pink-stained protoplasm, and rather flattened dark blue nuclei. Some of these cells show the hyaline portion divided in small round masses about the size of a red blood cell, and the nuclear material as pale blue spots. In others the cell membrane has disappeared and the round particles are scattered in the interstitial tissue (Fig. 27).

In the next group of polypi the hypertrophy is modified by the inflammatory process and is varied more from normal structure (Figs. 28, 29). The acini are tortuous or dilated and may show normal mucous cells or flat epithelium (Fig. 30). In other areas the acini show an infolding of the epithelium which may form subdivisions of the acinus (Fig. 31). Here the epithelium may change from the normal goblet cell to a still longer cell with large central nucleus and granular protoplasm. Some of these nuclei are dividing (Fig. 32). Still other acini may be prolonged toward the base of the polyp. These show several layers of cells which have lost their secreting character and masses of protoplasm occur which have more than one nucleus (Figs. 33, 34).

In still another group of polypi the stalk is more prolonged and narrow, and covered by the inflamed mucosa (Fig. 35). At the cauliflower-like extremity, however, we see some chronic inflammation and simple hypertrophy, but by far the greater number of acini show the marked abnormalities described in single crypts of the foregoing group (Fig. 36). That is, the acini are irregular and tortuous, with large columnar epithelial cells of undifferentiated type.

A further abnormal development is seen in the next two types of polypi. These are sessile and composed wholly of convoluted glands. In the first of these there are some crypts with normal mucous cells. But most of the glands have high columnar epithelium with actively dividing nuclei (Fig. 37). At the base of the polyp, where the dilatation and epithelial growth are most marked, some strands of epithelial cells have penetrated the basement membrane into the adjacent tissue (Fig. 38).

In the second type all the crypts are lined by an actively proliferating epithelium. Toward the base of the polypus the acini dilate and the epithelium and basement membrane project as irregular masses into the lumen which is filled with mucus and cell débris. Where these cavities invade the muscularis they are often imperfect and broken on one side (Fig. 39). The nodules of epithelium on the basement membrane may project either toward or away from the lumen (Fig. 40). The epithelium is of a definite vegetative character. The protoplasm stains deep blue, and is divided irregularly, often containing two or more deep black, or vesicular nuclei (Figs. 41, 42).

Many other polypi were examined in which the above described changes occur in varying degree and association. And it is to be noted that there are areas in the mucosa showing cancerous metamorphosis without polypus formation (Fig. 43).

In brief, we find in the stomach extensive chronic gastritis with multiple polypus formation. In these polypi we find associated with the gastritis, simple hypertrophy, benign and malignant adenoma, and cancer, with extensive invasion from multiple points of origin.

General Summary and Conclusions.

This case presents many unique features and is of interest, not only as a remarkable example of multiple heterologous tumor formation, but also as a basis for some generalization on the origin of tumors.

After a fairly wide examination of the literature, we were unable to find any like instance of multiple subcutaneous hæmangio-endotheliomata. Nor did we discover any record of a similar lymphangio-endothelioma formation throughout the entire intestinal tract. Lastly, also, we were unable to find any instance in which so many diverse types of epithelial tumor formation occurred in one stomach. So that, so far as we know, each of the three groups of tumors, present in this one case, is unique in the extent and character of its occurrence. And that all three should have occurred in one individual is truly remarkable.

It is inevitable that such an extraordinary coincidence of multiple tumors of different type in one individual should lead to some speculation as to possible common factors in their origin. We shall suggest therefore some hypothetical explanation of the facts observed.

Turning our attention, first, to the general picture, we find in an old man, with a marked alcoholic history, extreme generalized sclerosis of arteries, veins, and parenchymatous tissues. In the blood-vascular system we find an extreme grade of sclerosis affecting the aorta and larger arteries throughout the body, and a very marked phlebo-sclerosis, as well. In the subcutaneous tissue this sclerosis has resulted in obliteration of much of the stream bed and a compensatory formation of new vessels. These new blood-vessels are formed by the proliferation of the endothelium, as in granulation tissue. But in many places the endothelium loses its power of organization with a resultant exuberance of endothelial growth into cavernous angiomata. By a still further loss of this organizing force, the vegetative function of the cell predominates and we have the formation of solid endothelial tumors. The solid tumors may, in turn, give rise to metastases.

In considering the proliferation of the lymphatic endothelium in the intestine, we have no obvious factor, like the generalized sclerosis of the blood-vessels. It may be suggested, however, that the extreme portal obstruction, associated with the cirrhosis of the liver and the proliferative peritonitis and ascites, may play a part somewhat analogous. It may further be suggested that portal obstruction leads to over-loading of the lymph channels and that, in the attempt to compensate for the extra load, proliferation and new formation of lymph vessels may take place. Here again a loss of organization may lead to the development of cavernous angiomata and of solid endothelial tumors.

The changes in the gastric mucosa offer some points analogous to those considered in the discussion of the formation of the endotheliomata.

We may suggest a sequence here somewhat as follows: Cell destruction as a result of chronic alcoholism. Chronic gastritis as a protective effort on the part of the tissue. Regeneration in excess with polypus formation. And lastly, as a result of loss of organization, lawless growth with the production of adenoma and carcinoma, at many points simultaneously.

While the foregoing studies throw a certain, and we think important, light on the origin and method of tumor formation, it is equally certain that other factors, as yet unknown, play an even more important part in the determination of lawless cell growth.

No attempt will be made to give the extensive literature on the occurrence of multiple tumors. This field, in general, has been covered recently by Woolley (Bost. Med. and Surg. J., 1903, cxlviii, 1), while Versé (Arbeiten aus den pathologischen Institut zu Leipsig, 1908) has discussed exhaustively their occurrence in the stomach.

N. B.—In conclusion we wish to thank Professors L. F. Barker and W. S. Thayer for permission to use the case, Professor W. H. Welch for his interest and encouragement, and Dr. H. M. Evans for assistance in the injection of the specimens.

A REVIEW OF THE RECENT ADVANCES IN OUR KNOWLEDGE OF TROPICAL DISEASES.*

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When your secretary invited me to address your society, I accepted his invitation at once because I wanted an excuse to come to Baltimore. The invitation was accepted although I had no new piece of work sufficiently important and sufficiently interesting to you to furnish a subject for an evening's address; but I made up my mind to kill two birds with one stone and to bring my reading up to date by compiling from the literature an account of the most important advances which have been made in tropical medicine during the past year. It was hoped that it might be possible to entertain you for an hour by such an account.

It is quite unnecessary to remind you of the enormous amount of work which has been done during the past ten years, and still is being done, by workers in all parts of the world to elucidate the causation of tropical diseases. It is apparent to anyone who reads the ordinary medical journals that an enormous number of papers are published on subjects connected with tropical medicine. It is not so long since Rüge complained that it was quite impossible for one man to keep himself quite up to date in the literature of malaria alone; he may have exaggerated, but it certainly is almost impossible now for one man to read all that is written on tropical medicine and on the protozoa which cause so many of the diseases peculiar to warm climates. The number of papers on these subjects which appear in publications devoted to medicine in general—such as the *Lancet*, the *British Medical Journal*, the *Journal of the American Medical Association*, the *Deutsche medizinische Wochenschrift*, and so on—is not small; many more papers appear in the pathological journals —such as the *Centralblatt für Bakteriologie und Infektionskrankheiten*, the publications of the *Kaiserliches Gesundheitsamt* and the American laboratory journals; in addition to these there are a number of periodicals which are devoted solely to tropical medicine; they are, the *Journal of Tropical Medicine and Hygiene*, the *Annals of Tropical Medicine and Parasitology*, and the *Archiv für Schiffs- u. Tropenhygiene;* the *Bulletin de l'Institut Pasteur*, and the *Comptes Rendus de la Société de Biologie* and of the *Académie des Sciences*, as well as the *Proceedings of the Royal Society*, so frequently contain articles on tropical medicine that one almost places them amongst the journals reserved for the special literature of the subject. Sleeping sickness has a journal devoted to it alone, published by the British Sleeping Sickness Bureau. Its functions are to review all of the papers appearing on sleeping sickness and to spread information concerning that disease. One of the best of all of the publications dealing with tropical medicine is, of course, the *Bulletin de la Société de Pathologie Exotique*. Since it has been published, it has taken many of the papers which formerly went to the *Annales de l'Institut Pasteur* and to other French scientific journals. The transactions of the *British Society of Tropical Medicine and Hygiene* always contain extremely valuable papers.

In Great Britain, in the Philippines, in the Congo Free State, in Brazil, and in Portugal, there are institutions, more or less completely, devoted to research in tropical diseases; they periodically publish the results of their work in their own reports. The government and military medical services of, for example, the United States, Great Britain, and India, publish valuable reports; among the best of these are the scientific memoirs of the officers of the medical and sanitary departments of the government of India.

In addition to this huge mass of literature, reports are continually being published from expeditions sent out to study particular points in tropical medicine. Last year no less than

* Paper read before the Johns Hopkins Hospital Medical Society, February 21, 1910.

four important expeditions went to Africa to study sleeping sickness; all of them have issued isolated reports; one of them, in addition, has published a huge volume of 730 pages crammed with interesting information. Laboratories have been established at Khartoum and, more recently, on the West Coast of Africa at Lagos for the study of tropical diseases. The reports of the first named of these laboratories last year filled two large quarto volumes.

During 1909 at least three new text-books on tropical medicine saw the light and new editions of two others appeared. No less than three text-books were published on the pathogenic protozoa, one of them contained 900 pages, and two new handbooks of practical parasitology have been produced.

From this hurried enumeration of the publications dealing with tropical medicine, you will guess that it probably was necessary to winnow a good deal of chaff before it was possible to collect the few grains of corn which I hope to present to you this evening.

A good many papers which are published on subjects connected with tropical medicine are, in truth, chaff of the lightest description. For many years those who, for any reason, found it necessary to write original theses were accustomed to find an easy subject for their papers in the classification and re-classification of the malarial parasites. The work which followed the discovery of "MacCallum's Crow" has brought too much accuracy to our knowledge of malaria. Consequently its parasites are no longer a useful subject for these gentlemen, and many of them have turned their attention, instead, to the newer protozoan parasites. Anyone who tries to look at every paper which appears on, let us say the trypanosomes, the spirochætæ and the piroplasmata, cannot fail to be distressed in realizing how much good time has been wasted, how much good ink has been consumed and how many fair sheets of paper have been spoiled in producing unnecessary re-hashes of well-known facts concerning these parasites.

In 1898 the discovery that malaria is transmitted by the bites of mosquitoes awakened an interest which has resulted in the enormous amount of work on tropical medicine done since then. At first nothing was known of the rôle played by the protozoa, or by other animal parasites, in the production of tropical diseases; and it was most important to ascertain what were the parasites which occurred in tropical climates. Even in our own temperate climate we have come to realize that the diseases of men and of animals have everything in common; in the tropics this statement is truer than it is here. Although a parasite does not often parasitize both men and animals, it frequently happens that one species of a group of parasites is parasitic in man while another species of the same parasite has an animal host. Consequently it has frequently happened that a study of the parasites of lower animals has thrown valuable light upon important points in connection with organisms parasitic in man. For this reason it has been important to ascertain not only what were the parasites of men living in the tropics but it was also necessary to examine animals of all sorts in order to determine what parasites they might contain.

After a few years' work, it became quite apparent that all tropical animals possessed parasites of their own; and it was very evident that, for example, hæmatozoa—which are the most important of the pathogenic animal parasites—were common in almost every species of tropical animal. So soon as this fact was established our needs changed. A catalogue of the parasites infecting tropical animals ceased to be of any great value and the mere publication of the fact that a parasite of a certain appearance had been seen in man or animal was no longer of prime importance. This is especially so since it has become almost certain, from a study of the development of one or two of the pathogenic protozoa, that it is almost impossible to classify a hæmatozoon unless a part, at least, of its life history is known with some accuracy. Again, it has happened that a study of the life cycle of a parasite has led to the devising of measures by which the disease it causes can be successfully combated. For these reasons the greatest need of tropical medicine at the present moment is accurate knowledge concerning the bionomics of the pathogenic protozoa. In spite of this, perhaps because it is much easier, many observers are still spending their energies in mentioning the occurrence of parasites in strange beasts without making any attempt to ascertain how they get there.

I do not intend to speak of any of those tropical diseases which are caused by bacteria, or by food intoxication, as, for example, Malta fever, beri-beri, or pellagra; neither do I intend to mention any of those diseases which are caused by molds or fungi, and nothing will be said of the diseases produced by metazoan parasites. We shall consider only the pathogenic protozoa and our time will be almost altogether occupied by a consideration of the most important of them—the hæmatozoa. We shall, first of all, take a general view of the work done in the whole field of tropical medicine. We shall then consider what advances have been made in the technique employed in the investigation of tropical diseases and, lastly, we shall allude to the advances which have been made in our knowledge of a few particular diseases. I hope that I may be forgiven if I spend most time upon those which seem to me to be most important.

Through the publication of text-books and papers on subjects connected with tropical medicine and through the establishment of schools of tropical medicine, the number of well-trained medical men who practise their profession in the tropics has been greatly increased. One result of this increase has been that the existence of unusual diseases has been recognized in many new localities. For example, during the past year, Malta fever has been reported from the Upper Nile and from Marseilles; relapsing fever has been reported from Colombia, where it is transmitted by the bite of a tick of a different species from that which transmits the same disease in Africa. Relapsing fever has also been reported from Northern Africa. Kala-azar has been shown to exist in Northern Africa, in Italy and possibly also in Greece; while Delhi boil has been seen in several localities in Brazil, in Greece, and in Algiers.

Perhaps the most striking additions made to our knowledge of tropical medicine during 1909 have been (1) the dis-

covery of infantile kala-azar in Northern Africa and the work which has resulted from it; (2) the discovery of a new human trypanosome transmitted by a *Conorhinus* in South America; *and* (3) the knowledge which has made it almost certain that *Trypanosoma gambiense* does undergo a development in the tsetse fly which transmits it. (4) Typhus fever is perhaps not, strictly speaking, a tropical disease, but the fact that it can be transmitted to monkeys by the bites of body lice ought to be mentioned here, as well as the observation that a disease of Southern Austria, which greatly resembles dengue, is transmitted by the bites of a small fly (*Phlebotomus pappataci*).

Although no very extraordinary addition has been made to our knowledge, a great mass of work has been done during the past year on subjects connected with tropical medicine and much has been done to consolidate and coordinate what is known concerning them. Governments seem to have realized more completely than ever that the opening up of the tropics and their colonization by European races is entirely dependent upon the conquest of tropical disease; tropical countries cannot be colonized by Europeans until efficient means have been found of combating the maladies which make warm climates uninhabitable for Europeans. That governments do realize these facts has been shown by the active support which has been given to already existing institutions devoted to tropical research and by the establishment of new ones. For example, the government of Queensland has just established a laboratory for the investigation of the diseases occurring in Northern Australia; another example is the Commission of Entomologists which has just been appointed by the British Colonial Office to study insects which are connected with the transmission or production of diseases of men, animals, and plants in Africa. It is well that governments are alive to the importance of the study of tropical diseases and that new institutions are being maintained in many parts of the tropics for studying them; it is essential for the advance of our knowledge concerning these diseases that this should be the case because many of them are extremely chronic and our knowledge of them has reached a stage where it is almost impossible to advance it without studies lasting over periods of many months or even years. Continued work of this sort can only be undertaken by an institution; the length of time it requires and its tedious nature provide the best excuse for those individual workers who are contented with reporting the existence of a parasite in a host and who make no effort to ascertain something concerning its bionomics.

An enormous number of animals of all sorts have been examined during the past year to ascertain whether they were infected by hæmatozoa; as a result of this work, the presence of these parasites has been described in a great number of animals. One of the most complete pieces of work of the year was done upon a hæmogregarine of the rat by Miller; he described the parasite very carefully and fully worked out the most interesting cycle of development by which it is transmitted from rat to rat by means of the bite of a rat mite. An extraordinary number of trypanosomes have been reported in the blood of fish and other cold-blooded animals, in birds and in mammals. Most of these trypanosomes have occurred in tropical animals, but trypanosomes have been found in the blood of wild rabbits in Scotland and in the blood of wild rabbits and bush rats in Canada. Large trypanosomes, possibly forms of *Trypanosoma theileri*, have been seen in the blood of cattle in Germany, in the United States and in Canada. Some of the amœbæ and flagellate parasites which exist in the alimentary canals of small animals and of insects have received considerable study. New facts concerning an interesting disease of fowls, which is caused by a spirochæta and transmitted by a tick, have been obtained in Brazil, in Roumania, in the Soudan and in Senegal. One form of Leishmania, the parasite causing kala-azar, has been frequently found in African dogs and another parasite of the same species has been seen in African rodents. Some observers have found support for Schaudinn's famous observations on the alternation of generations in the occurrence of a parasite much resembling a trypanosome which has been found within the red blood cells of a South American edentate, and in the fact that one observer has stated that, in fresh preparations, he saw a living trypanosome of the lizard transform itself into a leucocytozoon. Spirochætæ have been described as a cause of a form of human bronchitis in Ceylon; and in Peru small bodies occurring in the red blood cells have been mentioned as a possible cause of the extraordinary "bleeding warts"—the *Verruca peruviana*.

Although the value of much of this work is comparatively slight, it has, nevertheless, helped to extend our knowledge in at least two directions: through it much has been learned concerning the distribution of parasitic disease and our knowledge of the general rules which govern the life activities of the protozoa has been augmented.

No great advance has been made in laboratory technique; the methods by which we have gained the greatest part of our knowledge of the pathogenesis of tropical disease have been very simple. Patience, a pair of dissecting needles, Romanowsky's stain and a good microscope have been, and for that matter still are, the most important part of the equipment of a laboratory devoted to the investigation of the pathogenic protozoa.

The importance of culture methods in the study of the pathogenic protozoa has been vindicated once more by the reproduction of infantile kala-azar in dogs by means of cultures of its causative parasite. The importance of cultural methods has also been shown by the detection and isolation of *Trypanosoma americanum* in the United States in cattle in which the existence of a trypanosome was not suspected. An important change in the ideas governing research work on tropical diseases has been the wide-spread realization of the fact that the methods of preparing parasites for microscopic examination, by which they are permitted to dry, are not good methods; if a delicate parasite be allowed to dry, it is subjected to a physical violence which inevitably alters its appearance. If it be desired to study the finest morphological changes in a protozoan parasite, it is necessary that it should

be prepared for examination by the most careful cytological methods. The material studied must be fresh, it must be well fixed, and it must never be permitted to dry, nor must it be subjected to sudden changes of osmotic tension by being quickly passed through solutions of widely differing density. Consequently "wet methods," by which preparations are not allowed to dry while they are being fixed, stained and mounted, have come to be generally used in the study of the pathogenic protozoa. The spread of the realization of the vital importance of studying living parasites in fresh preparations has constituted another advance in our laboratory methods. The majority of those who study the parasites causing tropical diseases have come to realize that the observation of an actual occurrence in a living parasite is definite and conclusive and that such an observation outweighs any number of observations, apparently negating it, which have been made from fixed material. This fact is probably a partial cause of the present tendency to accept, at least part of, Schaudinn's observations on the alternation of generations in the development of *Hæmoproteus noctuæ* and of *Leucocytozoon ziemanni*.

It will be remembered that in 1903 Schaudinn published a paper in which he described complete life cycles in each of these parasites. The forms of the parasites which had been previously known were both parasites of the red cells of the birds with which he worked; Schaudinn described extracellular, flagellate, forms for both of them; the hæmoproteus became a trypanosome and the leucocytozoon a spirochæta. Schaudinn's work met with a great deal of criticism; many observers did not hesitate to assert that he had been led astray by the existence of other parasites which are frequently present in birds and in the gut of mosquitoes and they believed that he had confused at least two, if not more, parasites in his description of the development of hæmoproteus and of the leucocytozoon. Schaudinn was, of course, a most careful and a most brilliant observer; in his memoir he definitely stated that he had seen certain changes take place in fresh preparations. Everybody knows how difficult it is to prove a negative; and one definite, positive, observation made by Schaudinn will outweigh a great number of negative observations made by less competent observers. This is particularly the case when the question is one concerning the pathogenic protozoa. Because, even under the most favorable circumstances, the most extraordinary patience is often necessary before, even fairly common, developmental forms of a protozoan parasite can be demonstrated.

Much of the work on tropical medicine has been done by medical men who are accustomed to work with bacteria; results are usually obtained much more quickly from work of this sort than from work done on the protozoa; consequently, many of the papers on tropical medicine which report negative results, and some of those which report positive conclusions, are evidently the result of work done with so little patience that one hesitates to accept their findings until they have been substantially confirmed. It is for these reasons that Schaudinn's conclusions have not been totally discredited although an enormous number of papers have been written to assail them.

The bibliography of sleeping sickness which has just been published by the Sleeping Sickness Bureau constitutes one of the most important works done on this disease during 1909; because of it, it is possible to say that our knowledge of sleeping sickness is better marshalled and more easily accessible than is the case with any other disease. Although no vital advance has been made in our knowledge of sleeping sickness, many small observations have been made which, when added to what was already known of the disease, give us a very fair knowledge of human trypanosomiasis and of the way in which it is transmitted. It seems as though there is no weak point by which the disease may be successfully combated as is the case with yellow fever and malaria; it seems to be one of those diseases which must be prevented, not by any one method, but by several. The work which has been done on sleeping sickness during the past year has been in three main directions: (1) the habits of the fly, *Glossina palpalis*, which transmits the disease have been studied in order to ascertain whether it would be possible to prevent the disease by exterminating it. At the same time a good many observers have tried to determine whether the trypanosome undergoes a developmental cycle in the body of the fly; (2) Ehrlich, and his co-workers, have been the foremost among a large number of persons who have made experimental and clinical attempts to treat the disease; (3) those who have been in charge of districts which were threatened by an epidemic of sleeping sickness have been particularly interested in the methods by which the disease might be most certainly and most quickly recognized.

Glossina palpalis is the most usual agent by which the disease is transmitted; a good deal has been learned about its habits. It was already known that it only lived near water and in localities where there was thick brush. The reason for this has been found in the fact that the singly deposited pupæ of the fly will not develop unless they are kept in a humid atmosphere and unless they are protected from the sun. These facts make it evident that all persons living in an infected country should avoid the neighborhood of water as much as possible and that watering-places and ferries, to which people must come, should be kept free from underbrush in order that there may be no shelter for the flies in their vicinity.

A good deal of work, which has resulted in no definite conclusion, has been done to ascertain whether *Trypanosoma gambiense* can be transmitted from man to man by other means than by the bite of *Glossina palpalis*. At the commencement of last year, most persons believed unquestioningly that the fly could only transmit the trypanosome if it had bitten an infected person not more than 48 hours previously. But when one considered the small quantity of blood ingested by each fly and the scantiness of trypanosomes in the blood of persons suffering from sleeping sickness, it became quite evident that the rapid spread of the disease in areas where it was epidemic could not be accounted for if

Glossina palpalis only transmitted the disease mechanically; that is if its proboscis merely acted as a hollow needle and if there were no development of the trypanosome within the fly. On entirely insufficient grounds Koch suggested that this discrepancy between the rapid spread of the disease and the inefficiency of the mechanical means of transmission might be accounted for through a transmission of the trypanosome by coitus. It has been shown since, that *Trypanosoma gambiense* may be mechanically transmitted by the bites of mosquitoes and it does not seem to be at all impossible that something of the rapid spread of the disease may be accounted for in this way; this explanation is scarcely needed now since it is very probable that a development of the trypanosome does occur within the fly because both the German and British expeditions have shown that *Trypanosoma gambiense* can be transmitted by *Glossina palpalis* up to a period of 75 days after the fly has fed upon an infected animal.

Although many observers have described appearances in preparations made from the gut of infected flies, which might be developmental forms, nothing definite can be said concerning them at the present time because of the frequency with which tsetse flies are infected with other flagellate parasites. Although flagellate parasites of the same sort frequently occur in the gut of the rat louse, it is practically certain that the ordinary trypanosome of the rat—*Trypanosoma lewisi*—does undergo a definite development in the body of the louse, by which it is transmitted. Some of the forms which have been described in the proboscis and in the alimentary canal of tsetse flies infected by *Trypanosoma gambiense* greatly resemble those which occur in the development of *Trypanosoma lewisi* in the rat louse. For this reason, and because of the length of time that the fly is infected after it has bitten an infected animal, it seems almost certain that *Trypanosoma gambiense* must undergo a development within the body of its invertebrate host. It is useless to speculate at present upon the nature of this development or to hazard a guess as to whether it is sexual or a-sexual.

A point well worth noting here is that not every fly which has bitten an infected person is capable of transmitting the infection after the lapse of 48 hours. A similar observation has been made in connection with the transmission of *Trypanosoma lewisi*. The development of the trypanosome does not occur in the body of every louse which has fed upon an animal infected with *Trypanosoma lewisi*. It is only when the trypanosomes are at a particular stage when they are ingested that the development occurs and it does not seem at all impossible that something of the same sort may occur in the transmission of *Trypanosoma gambiense* by *Glossina palpalis*. It may be that the development of the trypanosome does not occur in the fly unless the trypanosomes are ingested at a particular stage of their development. An analogy drawn from the well-known fact that only the adult male and female forms of the malarial parasite will develop within the body of an appropriate Anopheles suggests itself; and one asks whether it may not be that it is only in old-standing infections that *Trypanosoma gambiense* exists in man in a form suitable for undergoing a development within *Glossina palpalis*. The developmental change which the mammalian trypanosomes undergo, most frequently, in the circulation of their vertebrate host is a multiplication by binary division; but, it has long been known that these trypanosomes sometimes undergo a change in which the whole of the locomotary apparatus is lost. The analogy of a developmental cycle of the frog trypanosome suggests that this stage may be the first step in a process of multiplication of a different sort. In the frog trypanosome the flagellum, the undulating membrane and the blepharoblast are cast off. The organism becomes rounded and rapidly subdivides, dichotomously, until sixty or more small spheres result. Each of these divisions produces an undulating membrane and a flagellum, and passes through a herpetomomas-like stage to become a trypanosome. An observation made upon *Trypanosoma cruzi*, the new South American trypanosome, suggests that the supposition may be correct and that such a cycle of multiplication does exist in mammalian trypanosomes; it has been shown that *Trypanosoma cruzi* casts off its locomotary apparatus, becomes spherical and then divides so as to produce several new trypanosomes.

Through his work on the treatment of experimental trypanosomiasis, Ehrlich has arrived at far reaching conclusions in his study of "Chemical Constitution and Therapeutic Reaction." As he says himself, he hopes to see a day come when medical men will be in a position to "aim chemically" with the drugs which they administer in the treatment of disease. Ehrlich believes that the trypanocidal compounds of arsenic, which he has produced, owe their property of destroying trypanosomes to the fact that reduction has reached an extreme point in them. This view has not the complete support of those who believe that the trypanocidal effect is due to the formation of a body, called trypan-atoxyl, by a combination between the drug administered and some albuminous substance existing in the body of the host. Again, Ehrlich's view is directly combated by others who believe that atoxyl, for example, is oxidized in the bodies of animals treated by it. The practical result of the year's work on the treatment of human trypanosomiasis is that several, highly trypanocidal, compounds of arsenic have been produced and that preparations of antimony—particularly para-amido-phenyl-stibnic acid and tartar emetic—have been shown to be highly trypanocidal. At the present moment, the position in the treatment of human trypanosomiasis is this: the treatment is a dangerous one because the large doses of atoxyl necessary not infrequently cause neuritis, particularly optic neuritis and consequent blindness, but the treatment should nevertheless always be tried because it does offer a good chance for the recovery of early and thoroughly treated cases. Atoxyl and its derivatives are the most important of the trypanocidal agents. They are to be given in as large doses as possible and as early in the infection as possible. They should not be given in small doses or during a considerable period of time lest the trypanosomes become resistant to them. After a severe course of atoxyl has been given, the drug should be stopped and some

other trypanocidal drug should be given in order that the treatment may be a combined one; it has been definitely proved by experiments on animals that treatment by two trypanocidal drugs offers a greater chance of success than does treatment by a single one.

Long before Europeans commenced to study sleeping sickness, the natives of the West Coast of Africa realized that persons who had much enlarged neck glands very often died from sleeping sickness. From an investigation of the incidence of definitely enlarged glands among natives in the Congo Free State, it was concluded that every negro, suffering from enlarged glands, in an area where human trypanosomiasis existed, should be suspected of being infected with *Trypanosoma gambiense* until the contrary could be proved. This assertion at first met with a good deal of opposition but its accuracy has been confirmed by the results of the observations of the French Sleeping Sickness Commission and by the work done by an expedition sent out by the Liverpool School of Tropical Medicine to study that disease in British Central Africa. Now it is generally recognized that every native should be most carefully examined for trypanosomiasis if he be the subject of a glandular enlargement. This observation is exceedingly important because the history of the extension of sleeping sickness shows that it has been spread through Africa by the introduction of cases of the disease into formerly uninfected areas. By the establishment of modified quarantines in which cases of the disease will be isolated and treated, it is hoped that it will be possible, if not to prevent the existence of the disease, at least to delay its spread until more efficient means of combating it have been devised.

Leishman has confirmed the cycle of development of *Spirochæta duttoni* which the Liverpool observers described in the body of the tick, *Ornithodoros moubata*. It will be remembered that this spirochæta was observed to undergo approximately the same development in the bodies of its vertebrate and invertebrate hosts. It becomes coiled into a tight skein, its chromatic core fragments and new spirochætæ probably arise from the encysted chromatic masses which are thus produced. Leishman, in addition to confirming this development, has shown that the granules thus produced are infective when inoculated into experimental animals.

Additional support for this life cycle has been found in the study of *Spirochæta gallinarum*, which is transmitted from fowl to fowl by the bites of the tick *Argas persicus*. This spirochæta, like the *Spirochæta duttoni*, may enter the red cells of its vertebrate host; and, in the tick, it produces granules similar to those formed by *Spirochæta duttoni* in the human tick.

Relapsing fever is rather a dangerous disease to work with because of the numerous cases of laboratory infection which occur. A possible explanation of these cases, which formerly could not be accounted for, lies in the fact that *Spirochæta obermeiri* may be transmitted by rat lice.

Most of the publications which have appeared on malaria during the past year have dealt with the prevention of the disease. The methods by which malaria may be prevented, through the extermination of mosquitoes and through the destruction of the parasites in the human hosts by the public distribution of quinine, are familiar to everyone. The most efficient methods by which the principles of malaria prevention may be applied in communities of various types are rapidly becoming systematized. An excellent example of the complete success which follows an intelligent and thorough enforcement of anti-malarial measures is afforded by the health of the laborers employed upon the Panama Canal; the incidence of disease amongst those living in the Canal Zone is actually less than it is amongst the population of New York. Campaigns for the prevention of malaria have been carried on with almost equal success in other parts of the world; for example, mosquitoes have been practically exterminated at Port Said. It is interesting to note, in passing, that dengue fever has disappeared from Port Said with the mosquitoes; it was, of course, known that dengue fever could be transmitted by a Culicine mosquito. The French have realized that the success of their colonies in Northern Africa depends completely upon the prevention of malaria in them; and, consequently, the government has taken active measures against that disease. The extermination of mosquitoes is an important part of their propaganda but, as in Italy, those in charge of the campaign seem to lay especial weight upon the importance of cinchonizing the population through the distribution of quinine; a good deal has been written in Italy concerning the preparation of quinine which is best for public distribution. Because it has almost no taste and because it is easily absorbed, the tannate of quinine, prepared in chocolate tablets, seems to be the best form of the drug for this purpose.

Several important papers have appeared on blackwater fever. None of them have reached an absolute determination of the cause of blackwater fever, although a concensus of their opinions certainly supports the usual theory that blackwater is in some way the expression of an intoxication produced by chronic malaria. Consequently, if malarial parasites are present in the blood of the patient, quinine must be given; but, since quinine may sometimes precipitate a hæmoglobinuria, the drug must be given in small doses (2 grains); these doses are to be repeated, if necessary, at frequent intervals.

With the exception of the discovery of the infantile form of kala-azar, no particularly important addition has been made to our knowledge of that disease or of the parasite, *Leishmania*, to which it is due. The developmental stages of *Leishmania* formed in cultures by the parasite of kala-azar and by the nearly related parasite of oriental boil have been seen by several observers. No certain light has been thrown upon the possible relationship of these two diseases; it is interesting to note, however, that forms almost identical with *Leishmania donovani*, the parasite of kala-azar, have been found in the circulating blood of a patient suffering from an oriental boil, in which typical forms of *Leishmania furunculosa*, the parasite of oriental boil, had been demonstrated. The methods by which these diseases are transmitted have not been as-

certained although it has been suggested, not without grounds, that bed bugs—or perhaps a *Conorhinus*—might be the transmitters. Attempts at the treatment of kala-azar have been made and in some instances patients have undoubtedly improved under the administration of atoxyl; it is too early yet to say whether it is probable that this improvement may be a permanent one.

Very little has been added to out knowledge of yellow fever. Thomas succeeded in producing a distinct reaction, accompanied by fever and other symptoms, in chimpanzees and in guinea-pigs which were bitten by infected mosquitoes. Thomas believes that the illness produced by the bites of mosquitoes in these cases was yellow fever, and consequently, that it has been proved that the lower animals may suffer from that disease. If his conclusion proves to be correct, the observation is an important one.

A great deal has been written about the dysenteries, particularly about amœbic dysentery, and about the parasites which cause them; we shall say nothing of the bacillary dysenteries. An interesting observation is that there are apparently healthy "amœba carriers" just as there are apparently healthy typhoid carriers. An interesting treatment of chronic dysentery has been advocated by those who suggest that an appendicostomy should be done and that the opening should be utilized in applying frequent, copious douches to the whole course of the great bowel. The pathogenic properties of *Balantidium coli* have been once more proved by the observance of a severe dysentery produced by this parasite in monkeys; while *Lamblia intestinalis* has again been described as a probable cause of Cochin China diarrhœa.

Although it has so far been without practical result, one of the most interesting features of the year's work, in as much as it shows the probable trend of much of the future work on the pathogenic protozoa, has been the enormous number of papers which have appeared on subjects connected with the immunity which may be acquired against protozoan parasites. The position of our knowledge is, approximately, this: that an immunity—if not a "sterilizing immunity" at least a tolerance—may be acquired by many mammalian hosts to the presence of protozoan parasites. For example, those who have lived for many years in malarious districts may have the parasites of malaria in their bodies without suffering any apparent ill effects; just in the same way, some wild animals, and even cattle and, possibly, men, may live for many years with pathogenic trypanosomes circulating in their blood; while both in America and in the Tropics cattle infected with piroplasmata live healthily for years. In all of these diseases the "resistance" of the host, from some undefined cause, may be suddenly lowered. Then the host seems to be no longer able to resist; the parasite multiplies and produces an acute attack of the disease with which it is associated. The question which is to be solved is, what is the mechanism by which these hosts are able to keep the parasites infecting them in check for so long? The papers which have appeared so far have barely touched the fringe of the question and have made no attempt to reply to it. When it is answered, it is probable that it will bring us some indication of the direction which work must follow which has for it object the devising of means of preventing protozoa-caused diseases through the production of active or passive immunity in the hosts.

ANAPHYLAXIS AND ITS RELATION TO CLINICAL MEDICINE.*

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It was with much pleasure that I accepted the invitation of your secretary, Dr. Moss, to speak to the Medical Society of the Johns Hopkins Hospital upon the subject of anaphylaxis. In addition to appreciating the honor of the invitation of your secretary I was especially pleased to come, in view of the fact that the first paper that was presented in America upon the subject of anaphylaxis was one by Dr. Rosenau and myself, before the Association of Pathologists and Bacteriologists in this city in the spring of 1906.

The Johns Hopkins Medical School bears a peculiar relation to the subject of anaphylaxis in that Prof. von Pirquet, now professor of pediatrics at Johns Hopkins University, was the first to call attention to the manifestations of anaphylaxis in the human being. His work gave us our first understanding of the unpleasant serum reactions, and to him we owe a new disease—the serum disease.

* Read before the Johns Hopkins Hospital Medical Society, March 7, 1910.

In most of my work upon anaphylaxis up to this time I have been associated with Dr. Rosenau, and my remarks will be based largely upon this joint work.

The earliest experimental work upon the subject was that by Richet, working with actinia poison in dogs. Richet coined the word "anaphylaxis" from two Greek words ἀνά against, and φύλαξ guard, or φύλαξις protection. He considered the condition an opposite one to that of prophylaxis; but we now know that the phenomenon, instead of being a disadvantage, is probably an important step in the protection of the organism against a certain large class of infections.

The condition of anaphylaxis may be transmitted from the mother or may be acquired, and it may be brought about by the introduction of any strange proteid into the body. A well known clinical instance of anaphylaxis is that induced in an individual by a second vaccination. In the reaction to a primary vaccination the incubation period is about four days, *i. e.*, in about four days the local symptoms at the point of

vaccination appear or become distinctive and there is a more or less constitutional disturbance. In a secondary vaccination, or a vaccination following a successful vaccination after some months, the period of incubation is much shortened and the clinical reaction very much lessened. In other words, the power to react has been so changed that, instead of an incubation period of four days, we have an incubation period of 24 or 36 hours. This acquired power of immediate response is an evidence that protective bodies have been formed within the organism; but there is no absolute immunity in this class of infections though, on account of the power of immediate reaction, the individual is protected.

Other well known clinical instances of anaphylaxis are the tuberculin and mallein reactions in tuberculosis and glanders. Neither of these bacterial products is harmful in moderate amounts to a healthy individual, but a person suffering from tuberculosis or glanders will respond to a very small amount of tuberculin or mallein respectively.

It has been known since the seventeenth century that the whole blood of certain animals is poisonous when transfused or injected into man. Many workers have found that the blood serum of an animal of one species is frequently poisonous when injected into an animal of another species, but that the serum of the horse and the donkey to a large extent lacks such poisonous properties. Large amounts of horse serum may be injected into man, the rabbit, the guinea-pig and other animals without causing very unpleasant results except possibly a slight reaction at the site of inoculation. In a certain proportion of cases, however, the injection of horse serum into man is followed by the syndrome described and named by von Pirquet as the "serum disease." In a very small percentage of cases the injection of horse serum into man has been followed by sudden death.

Horse serum, when injected into guinea-pigs, is a comparatively bland and innocuous substance, but these animals may be rendered so sensitive that a second injection of horse serum may produce death, or at least very severe symptoms.

If a guinea-pig be given 0.001 cc. horse serum and 14 days later a second injection of a larger amount the result is almost invariably fatal. The same will be true if the animal at the two injections be given some other protein such as eggwhite or milk, or some vegetable protein such as edestin or excelsin.

The first injection of the foreign protein has so changed the mechanism of the animal's organism as to render it very susceptible to the second injection. A certain time must elapse between the first and the second injection in order that this hypersusceptibility may be manifested. This time varies from 5 to 12 days and is in close accord with the period of incubation of the "serum disease" which von Pirquet places at 8 to 13 days.

As the first experimental work with anaphylaxis was done with horse serum it was thought that diphtheria antitoxin had some part in this toxic action of the serum; but as it was soon found that the phenomenon could be induced by any protein, such as those which have just been named, it was seen that diphtheria antitoxin had absolutely no part in the production of the phenomenon.

The toxic action following the injection of the serum is due to a protein in the horse serum and is entirely independent of the antitoxic properties of the serum. It would be exceedingly unfortunate if the studies upon anaphylaxis should in any way prevent the usage of diphtheria antitoxin, or any other therapeutic serum, when it is indicated.

Most of the studies upon anaphylaxis have been done upon guinea-pigs, using horse serum as the foreign protein. And in discussing the subject I shall speak of horse serum, using it, however, in the sense of a protein.

The symptoms produced by the injection of horse serum into a susceptible guinea-pig are exceedingly characteristic. They are apparently the same, whether the animal be given the injection subcutaneously, intravenously, intraperitoneally or into the brain, with, however, the difference that when given into the brain or into the circulation the symptoms appear very much more quickly and frequently with explosive violence, in some instances the animal dying within three minutes after the injection. Within 5 or 10 minutes when the injection is given intraperitoneally the guinea-pig becomes restless and agitated; it runs about the cage, and sometimes utters sounds of distress; then there appear manifestations of peripheral irritation and respiratory embarrassment as shown by scratching at the mouth, coughing, sneezing, rapid and irregular respiration. An exceedingly characteristic feature of the respiratory involvement is that at intervals the animal makes an unusually deep inspiratory effort with the diaphragm, resulting in a marked sinking at the lower end of the sternum. The stage of excitement is soon followed by one of paresis, or in some cases complete paralysis. The animal is unable to stand and if it attempts to do so it falls upon its side. Spasms or general convulsions may now appear.

Guinea-pigs in a condition of complete paralysis may fully recover, but within a short time convulsions usually begin and are almost invariably a forerunner of a fatal termination. Occasionally in guinea-pigs not very susceptible the onset of the symptoms following an intraperitoneal injection may be delayed 30 or 40 minutes, but in only a few instances have I noted the onset of symptoms delayed as long as one hour.

The chain of symptoms is exceedingly characteristic, but they do not always follow the same order. Death usually occurs following an intraperitoneal injection within 30 minutes. There appears to be no lowering of the animal's temperature during or following the appearance of the symptoms. There is a marked fall in the blood pressure, which goes hand in hand with the respiratory embarrassment. The blood during this stage is very dark in color and there is a tendency to delayed clotting. If, when the respiratory embarrassment is marked, the animal be given artificial respiration there is almost immediately a rise in the blood pressure.

After complete cessation of respiration the heart continues to beat for a long time. In some instances I have noted the heart to beat as long as 30 minutes after complete stoppage of respiration.

Death is apparently due to asphyxia and, as suggested by Auer and Lewis,[1] is probably a result of a tetanic contraction of the muscles of the bronchiolæ and alveolar ducts, thereby preventing the free ventilation of the alveolæ.

The hemorrhages which have been described by some as characteristic lesions in death from anaphylaxis are probably due, not to a rupture of the capillaries, but to an oozing following the very great lowering in blood pressure and are not characteristic of death from anaphylaxis alone.

At least a certain time must elapse between the first and the second injections of the protein before the anaphylaxis is manifest. This time or period of incubation is from 7 to 12 days, which is about the same as for the serum disease in man and is very similar to the period of incubation of a number of the infectious diseases.

I have noticed suggestive symptoms in guinea-pigs when the second injection is given after an interval of four days and have found the animal sensitive after an interval of over three years. The optimum period or interval, however, for the development of anaphylaxis is after three weeks.

If the guinea-pig be given an injection of a foreign protein and then a second injection at any time during the period of incubation no ill results will follow; in other words, there has not been time for the body to become sensitive to the second injection. But if the second injection be given after the 12th day the animal is then found to be acutely sensitive to the second injection, and the result is usually fatal.

There appears to be no difference whether the animal be given the sensitizing injection subcutaneously, intraperitoneally, into the brain or into the circulation, or whether the intoxicating dose be given through the same or through different channels.

In the first paper by Rosenau and myself[2] we suggested that the portion of the protein which sensitizes the guinea-pig is the same as that which later poisons it, and up to the present no work has appeared to cause me to alter this opinion.

Wells[3] has brought forward experimental data to show that the two are at least in the same protein molecule or are two separate portions of the same molecule. Some workers have claimed that as heat and other agents had a different effect upon the sensitizing and toxic principles in horse serum the two principles were different; but it has been shown[4] that, while the toxic and sensitizing action of serum is gradually modified by heat when the serum is in a liquid condition, these principles are practically unaffected when the serum is first dried, then heated, redissolved and used either for sensitization or intoxication.

It would seem that these workers have fallen into the error of drawing conclusions as to the different effect of various agents upon the sensitizing and poisoning properties of proteins by overlooking the fact that, while it requires a very minute amount of the protein to sensitize, it requires considerably larger amounts to intoxicate the guinea-pig; and if a portion of the anaphylactic-producing properties of the protein is destroyed by some means there might be enough left to sensitize an animal in certain amounts but not enough to intoxicate except in amounts very much larger than those commonly used.

The effect of heat in modifying or destroying the anaphylactic properties of proteins depends upon its effect, as suggested by Wells[5] and later proved by Anderson and Rosenau,[6] in rendering the proteins insoluble rather than by the production of chemical changes in the proteins. For example, if the horse serum be heated in the liquid state, its sensitizing and intoxicating properties are gradually lessened by heating from 60° C. until at 100° C. they are practically destroyed. But if the serum, and the same is true of a protein such as eggwhite, be thoroughly dried, it may then be heated to temperatures as high as 170° C. for 10 minutes or 130° C. for two hours without affecting to any appreciable extent its anaphylactic properties when redissolved in salt solution and injected into a guinea-pig.

Neither sensitizing nor toxic principles in proteins are affected by various substances such as calcium chloride, sodium nitrate, magnesium sulphate, ammonium sulphate, formaldehyde, pancreatin, rennin, invertin, emulsin, malt, etc., nor by freezing, filtering through porcelain, precipitation and dialysis, or exposure to the X-rays.

Lewis and Auer[7] reported that atropine appeared to have a favorable influence upon the outcome of anphylaxis when given a short time previous to the intoxicating injection. With Dr. W. H. Schultz, of the Hygienic Laboratory, I have been able to confirm to a certain extent these observations; but apparently the amount of atropine needed for guinea-pigs is so large that it does not seem to promise much for its practical use in man when used in individuals known or suspected of having an idiosyncracy for horse serum, but further work with the substance may alter this view.

We[8] have found that, working with very sensitive guinea-pigs, it was possible to save with atropin sulphate about 28 per cent, with injections of chloral hydrate plus urethane and adrenalin 41 per cent, by administering pure oxygen 43 per

[1] Auer, J., and Lewis, Paul A.: Acute anaphylactic death in guinea-pigs; a preliminary note. J. Am. M. Ass., 1909, Vol. LIII, p. 458.

[2] Rosenau, M. J., and Anderson, John F.: A study of the cause of sudden death following the injection of horse serum. Hygienic Laboratory Bulletin, No. 29.

[3] Wells, H. Gideon: Studies on the chemistry of anaphylaxis, I. J. Infec. Dis., 1908, Vol. V, p. 449.

[4] Anderson, John F., and Rosenau, M. J.: Further studies upon the phenomenon of anaphylaxis. J. Med. Research, 1909, Vol. XXI, pp. 1-19.

[5] Wells, H. Gideon: Studies on the chemistry of anaphylaxis, I. J. Infec. Dis., 1908, Vol. V, p. 449.

[6] Anderson, John F., and Rosenau, M. J.: Further studies upon the phenomenon of anaphylaxis. J. Med. Research, 1909, Vol. XXI, pp. 1-19.

[7] Lewis, Paul A., and Auer, John: Acute anaphylactic death in guinea-pigs; its cause and possible prevention. A preliminary note. J. Am. M. Ass., 1909, Vol. LIII, p. 458.

[8] Anderson, John F., and Schultz, W. H.: The cause of serum anaphylactic shock and some methods of alleviating it. Proc. Soc. Exper. Biol. & Med., 1910, Vol. VII, pp. 32-36.

cent, and by administering pure oxygen along with chloral hydrate and adrenalin even 66 per cent. Almost invariably life was prolonged, the pigs eventually dying from low blood pressure and not from acute asphyxia.

It requires only a very small amount of horse serum to sensitize a guinea-pig. Amounts as small as 1/1,000,000 cc. will do this, or 1/20,000,000 part of purified eggwhite, while 1/100 cc. of horse serum intravenously or 5/1000 mg. of purified eggwhite are fatal to a sensitive animal.

Besredka [9] has reported that anaphylaxis may be prevented by ether or alcohol narcosis.

Banzhaff and Famulener [10] have also reported that the administration of large doses of chloral hydrate to guinea-pigs prevents death from anaphylaxis in a large proportion of cases.

These procedures have always appealed to me as being theoretically very advantageous, as they might act in one or two ways; either by a blunting of the respiratory center so that it would not respond to the extreme shock of the substances formed by the union of the intoxicating dose and the previously formed antibody, whatever it may be, resulting from the first injection of the serum, or by relaxing the muscular fibers of the bronchioles thus admitting a free exchange of oxygen. But later experiments have shown that these reported results are not borne out by other workers, for the fatal outcome of anaphylaxis is not prevented by ether or alcohol narcosis or by the administration of large doses of chloral hydrate, urethane, or other similar preparations.

From the beginning of my work upon anaphylaxis I was interested in the specificity of the reaction and had often in my mind the possibility of the utilization of this specificity in medico-legal work and also as an aid in the diagnosis of certain diseases by the passive production of anaphylaxis.

For proteins of a very different nature the anaphylactic reaction is absolutely specific, but for proteins more or less closely related, such as that in the serum of a horse and the serum of a dog, the reaction is only quantitatively specific. That is, the animals may respond to an injection of the heterologous serum, but the reaction is never as marked as when the homologous protein is given at the second injection. But there is the possibility that if the passive method be used this reaction, even with related proteins, may be found to be strictly specific.

A very interesting fact in connection with the specificity of the reaction is that guinea-pigs may be sensitized with three proteins at the same time. That is, they may be given a mixture of eggwhite, horse serum and milk at the same time, and then tested for their susceptibility to each one of these substances and found to react after the usual incubation period to a second injection of each substance at intervals of about two hours. In other words, the animal differentiates the anaphylactic-producing substances in a separate and distinct manner and is found to be susceptible to a second injection of each one of the three substances in the same way that an animal is susceptible to three separate infectious diseases.

Gay and Southard [11] discovered that there is a substance in the blood of sensitive guinea-pigs that may be transferred to a normal guinea-pig and render it susceptible to a subsequent injection of the protein 15 days later.

Otto [12] later showed that this passive sensitization was apparent within 24 hours.

Gay and Southard gave the name "anaphylactin" to their principle and considered it a portion or "rest" of horse serum. In this they are probably correct, but the passive sensitizing substance shown by Otto to be present within 24 hours is very probably an antibody. On account of its power of producing a changed reaction and the necessity for a name I should like to propose the name *allergin* for this passive sensitizing principle which is manifest within 24 hours, in contradistinction to the anaphylactin only manifested within 15 days.

It has been found that *allergin* does not appear in the blood of sensitized guinea-pigs until the 9th or 10th day, *i. e.*, just about the expiration of the period of incubation. It is found not only in the blood of sensitive guinea-pigs, but in the blood of guinea-pigs that have received a number of injections of serum sufficient to render them either immune or extremely refractory to a single large injection.

From this it would appear that there can be produced a cellular immunity to anaphylaxis, while the sensitizing substance (*allergin*) is present in the flowing blood, the organism as a whole or its susceptible cells being protected by a neutralizing antibody.

When guinea-pigs are sensitized with three proteins at the same time, three separate *allergins* may be demonstrated.

Many workers have studied the question as to the presence of an antibody in the blood serum of sensitive guinea-pigs, but without having satisfactorily demonstrated its presence.

One of the most interesting facts brought out in our studies upon anaphylaxis and which, in my mind, has been much neglected in later work upon the problem, has been the sensitization of guinea-pigs by feeding them for several days on the foreign protein. Guinea-pigs may readily be sensitized by feeding them a protein for several days; when tested for their susceptibility after 14 days by an injection of the protein they are found to be sensitive.

Wells [13] has found that the specificity is lost when certain proteins are fed to men, their urine collected and used to sensitize guinea-pigs. He found that when alimentary albuminuria is produced in man by feeding raw eggs and the urine of the individual used to sensitize guinea-pigs, the latter animal will not respond to a second injection of eggwhite, but develops anaphylaxis when given an injection of human ascitic fluid. This has an important relation to the sensitization of

[9] Besredka, A.: Comment peut-on combattre l'anaphylaxie? Ann. de l'Inst. Pasteur, 1907, Vol. XXI, p. 950.

[10] Banzhaff, E. J., and Famulener, L. W.: A note on anaphylaxis. Proc. Soc. Exper. Biol. & Med., 1908, Vol. LXII.

[11] Gay, Frederick P., and Southard, E. E.: Serum anaphylaxis in the guinea-pig. J. Med. Research, 1907, Vol. XVI, p. 143.

[12] Otto, R.: Zur Frage Serum-Ueberempfindlichkeit. Münch. med. Wchnschr., 1907, Vol. LIV, p. 1665.

[13] Wells, H. G.: Alimentary albuminuria by means of the anaphylaxis reaction. J. Am. M. Ass., 1909, Vol. LIII, p. 863.

animals by feeding them with the foreign protein, and may give us some insight as to why certain individuals have a peculiar idiosyncracy for certain articles of diet; also, why certain individuals who have never previously received an injection of foreign protein should be so acutely sensitive to a first injection of horse serum.

Another exceedingly interesting point brought out in the early work was as to the maternal transmission of anaphylaxis. It was found that the young of a female guinea-pig which had received an injection of horse serum, either before or after conception, were acutely sensitive to an injection of the same protein. This transmitted sensitiveness is solely maternal; the male takes no part in it.

The milk has been excluded as a factor in this transmitted susceptibility by a number of exchange experiments, which consisted in placing the young guinea-pigs born of a susceptible mother to nurse with an untreated female and, in exchange, the young of the untreated female to nurse with a susceptible female. From these experiments it was learned that the hypersensitiveness is not transmitted in the milk.

These experiments upon the transmission of anaphylaxis by the female to her young are of very great interest in relation to the question of an inherited tendency to tuberculosis in children born of a tuberculous mother. It is generally accepted, I believe, that the children of a tuberculous mother, instead of having an immunity to tuberculosis, on the other hand are more susceptible. I think it can be stated positively that only very rarely is the child born with the seeds of the disease in its system, but that there is transmitted from the mother to her offspring a tendency to the disease.

There appears to be a very close analogy between the tuberculin anaphylaxis and the anaphylaxis produced by the injection of proteins. The one is an anaphylaxis produced by the products of bacteria growing in the animal body, and which may be manifested by an injection of the products of the same bacteria growing outside the body; the other is an anaphylactic condition produced by the injection of a protein, and may be shown after a certain interval by a second injection of the same protein.

In the case of protein anaphylaxis this hypersusceptibility is transmitted by the mother to her young. In the case of tuberculosis the disease itself is not transmitted by the mother to her offspring, but the tendency to the disease is. I think here is a very promising field for work.

In certain cases in which the mother has received an injection of serum before the birth of the child a hypersensitiveness may be transmitted to her offspring, and this may explain some of the severe primary reactions in children.

There can be hardly any question but that man may be sensitized in the same way as has been shown to be the case with guinea-pigs. Repeated injections of horse serum into man at intervals of days, months or even years are not infrequent. Persons exposed to or suffering with repeated attacks of diphtheria are given injections of antitoxic serum at short or frequent intervals. It is not unusual for persons to have several attacks of diphtheria at longer or shorter intervals or to be exposed to diphtheria, and to be treated each time with diphtheria antitoxin.

The method of use of certain sera, as for example the antitubercule serum of Maragliano, require their administration at intervals of days or weeks continued over a long period of time. In all these cases of repeated injections the amount which has been injected, the interval between the injections and the number of injections must be taken into consideration. von Pirquet and Schick,[14] in their work upon the serum disease, found that when the second injection was given after an interval of 14 days to four months they obtained what they termed their "immediate" reaction, in which the symptoms of the serum disease appeared at once or within 24 hours; but that when the interval was more than four months, they obtained little or no immediate reaction but what they termed the "accelerated" reaction, in which the symptoms of the serum disease appeared on the 5th, 6th, 7th, or 8th days. It will be remembered that the usual period of incubation is from 8 to 13 days.

Guinea-pigs show practically no reaction following a single injection of serum, while in man the symptoms of the serum disease may appear after an incubation period of 8 to 13 days. Both man and the guinea-pig react to a second injection; the reactions in man and the guinea-pig, however, differ to some extent both in severity and in kind. The reaction following a second injection into the guinea-pig is, to a large extent, borne by the respiratory system, whereas in man the reaction is shown locally at the point of inoculation, by fever, by joint pains, swelling of the lymph nodes, and albuminuria. In a few cases in man, however, the reaction is very similar to that in the guinea-pig and these cases are the alarming ones.

In rabbits the reaction is rarely manifested after a second injection, but may be brought out by repeated injections at intervals of days. Some of the fatal cases in man, other than those following the first injection, have been in persons who have received repeated injections at intervals of days over a period of some time, thus being somewhat similar to the reaction in the case of the rabbit.

It was suggested by Besredka[15] that there might be a relation between the toxicity of serum, as tested upon guinea-pigs, and its power to produce the serum disease in man. But work by others has shown that the symptoms of the disease depend largely upon the amount of serum used and the interval between the injections. The unfortunate accidents, such as collapse and sudden death, depend to my mind more upon individual sensitization than upon the so-called toxicity of the serum used. It has been found that serum which has not produced untoward symptoms when injected into man is fully as toxic for sensitive guinea-pigs as serum, the use of which has been followed by serious symptoms or even sudden death when injected into man. As before stated, I believe it de-

[14] von Pirquet, C., and Schick, B.; Die Serumkrankheit. Leipzig, Franz Deuticke, 1905, 144 p.

[15] Besredka, A.: Toxicité des sérums thérapeutiques, sa variabilité et son dosage. Ann. de l'Inst. Pasteur, 1907, Vol. XXI, p. 777.

pends upon the susceptibility of the individual and not on the toxicity of the serum.

It has been a most interesting fact, in this connection, that many of the cases of sudden death following the first injection of serum in man have been in asthmatics or in persons who have an idiosyncracy to horses. That is, there are certain individuals who show peculiar symptoms, sometimes resembling hay fever or asthma, when in the vicinity of horses or horse stables; and these individuals are the ones who are so extremely susceptible to a first injection of serum. The knowledge of the fact that the injection of horse serum into such persons is a danger must certainly be taken into consideration in the use of antitoxin.

Anaphylaxis having been produced by various proteins, and the similarity of the tuberculin and the mallein reactions to protein anaphylaxis, early suggested the possibility of the production of anaphylaxis by bacterial extracts. It was thought that perhaps following anaphylaxis produced by bacterial extracts, there might be an immunity to the corresponding bacteria. In certain instances this has been found to be true.

I am of the firm opinion that the phenomenon of anaphylaxis has an important relation to the prevention and cure of certain specific processes and that resistance to certain diseases is largely gained through the processes of hypersusceptibility, and this opinion is certainly strengthened by the immunity which follows a hypersusceptibility developed by bacterial extracts. It is not more than a coincidence that the time required for the development of anaphylaxis corresponds very closely with the period of incubation of a number of infectious diseases and with the period of incubation of the serum disease.

In certain diseases with short periods of incubation, such as pneumonia, the crisis which commonly appears about the 8th to the 10th day may find a somewhat similar explanation.

It is also equally evident that those diseases produced by soluble toxins, such as diphtheria and tetanus, do not belong to this class.

It is very evident from the above rather incomplete review of the subject of anaphylaxis that studies upon this phenomenon are of more than theoretical interest and value, and that a satisfactory explanation of the mechanism of anaphylaxis will give us a clearer insight into the cause of recurrence of and resistance to a certain class of diseases.

AN UNUSUAL CASE OF CEREBRAL TUBERCULOSIS FOLLOWING TUBERCULOUS OTITIS MEDIA.*

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J. N., colored, three and a half years of age, was brought to the dispensary of the Baltimore Eye, Ear and Throat Charity Hospital April 5, 1909, with the following history: When about two years old his mother first noticed a purulent discharge from the left ear; there was no apparent preceding discomfort or febrile condition. The family physician was consulted but a profuse otorrhœa persisted in spite of treatment by irrigation and an operation, performed at one of the hospitals, through the external auditory canal, consisting probably, from the parent's description, in the removal of a polyp. In January, 1909, the child commenced to have muscular twitchings of the left side and spasmodic movements of the left leg and arm, followed by a growing inability to use these limbs. Such attacks recurred at irregular intervals, with increasing frequency, until on April 4 there was a pronounced convulsion; the spasmodic movements then involved the entire body but, the mother thought, began in the left leg and continued more pronounced on the left side; there was slight, if any, retraction of the head and the child made no outcry, though it was not completely unconscious. The attack began at 4 p. m. and lasted two hours or more, with short intervals of quiet. Suspecting a connection between the convulsions and the ear disease, the family physician advised sending the child to the hospital.

On admission, the child appeared to be of normal size but poorly nourished. He was perfectly conscious, rather apathetic, understood and obeyed simple questions and commands, and showed no irritation at the examination. The head was persistently held to the right but there was no retraction and no stiffness of the neck. Voluntary movements of the right leg and arm were freely made but he showed no inclination to move the left leg and, when the left arm was moved, supported it with the right hand. On manipulating the left leg or arm there was at first a feeling of limpness which at once gave way to a spastic condition in which extension and flexion of the joints seemed retarded, as if the joints were stiff. The left eye could be closed but there was a condition of lagophthalmos and when observed later, in sleep, the eye was partly open. Ophthalmoscopic examination showed nothing of importance; it was thought at first that there was a slight venous congestion but repeated examinations led to the conclusion that this was a mistake. The temperature on admission was subnormal, 97.5° F.

Before referring to the aural examination it may be well to present the notes of the neurological investigation made the following morning by Dr. Henry M. Thomas, who was kind enough to examine the patient for us. In brief, his report was

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as follows: "Patient lies with the head drawn to the right but if turned to the left does not seem to suffer any pain. The neck is a little stiff but the head can be turned in all directions without giving any discomfort. Visual axes equal and ocular movements good. Pupils small but respond to light. Reflexes: Abdominal, active on right, present but not marked on the left. Cremacteric active on both sides but more marked on the left; tendon Achilles active on both sides but more so on the left; patellar active on both sides, suggestion of a clonus on the left; plantar stimulation causes response on both sides, as does also descending tibial pressure. Kernig's sign absent; Babinsky's and Oppenheim's negative. Diagnosis: Left hemiparesis with active reflexes."

Aural examination: Right ear perfectly normal. Left external auditory canal filled with pus that seemed to form almost as rapidly as it could be wiped away. The tympanic membrane and ossicles apparently completely destroyed and the tympanic cavity partially filled with granulation tissue. In the superior wall of the canal, close to the annulus, a fistulous tract from which pus could be seen oozing into the canal and pressure above the auricle, over the squamous portion of the temporal bone, increased this flow. The preauricular and supramastoidal glands were considerably enlarged and pressure over the antrum caused some little pain, though the tenderness was either not of high degree or the child was not in a very sensitive condition. Pus from the ear showed a mixed infection, pneumococci predominating, but a few streptococci and some bacilli that morphologically resembled tubercle bacilli were seen; with a special stain one slide showed what was believed to be a single specimen of the tubercle bacillus, but repeated efforts later, failed to produce more positive evidence of this and, unfortunately, cultures were not successfully grown.

The blood examination showed a leucocytosis of 12,500, in which the differential count gave 60 per cent of polymorphonuclear cells.

A lumbar puncture gave a perfectly normal spinal fluid; clear in color, under no pressure, and smears and cultures made from it proved negative.

The Calmette conjunctival tuberculin test was employed, with no resulting reaction.

There having been no recurrence of the convulsions and no markedly urgent symptoms the patient was kept under close observation for the next four days. During that time the temperature varied from 99° F. to 102° F.; there was no nausea and no apparent suffering; the principal symptoms were fever and a profuse discharge of pus from the ear.

From the above history and examination, it was apparent that we had to deal with a chronic suppurative otitis media, possibly of tubercular origin, which had certainly invaded the mastoid and probably the intracranial structures. An operation was certainly indicated but how extensive would it probably be? The fever, profuse discharge of pus, fistula in the external auditory canal and partial facial paralysis did not necessarily mean anything more than mastoiditis. The convulsions and the paretic condition of the left side were difficult to explain; the first might be due to a general septic condition accompanying mastoiditis or to an extradural collection of pus; the increased intracranial pressure produced by the latter lesion might explain the existence of both the convulsions and the paresis. Leptomeningitis was ruled out by the normal condition of the spinal fluid. A cerebral abscess was considered possible but there were no strong supporting symptoms; only once, at the time of admission, had the temperature been below normal and that was readily accounted for otherwise; a differential blood count did not indicate it; there were no localizing symptoms; the muscular impairment of the left side suggested a cerebral lesion on the side of the brain opposite the affected ear, but we have previously reported a case in which typical Jacksonian convulsions were caused by an extradural abscess of the same side. The only possible conclusion then seemed to be to perform a mastoidectomy and explore the base of the brain through this wound.

The operation was performed April 10 and proved very interesting. An incision through the soft parts was made slowly, layer by layer, as is our custom, and in this instance it was particularly well that the general advice, to plunge the knife down to the bone at once and make an incision completely through all the soft structures and the periosteum at one cut, was not followed for by so doing the brain would almost surely have been injured; in cutting the deeper subcutaneous tissues there was a sense of giving way before the pressure of the knife blade as though there was no bony support, and this was practically the case. When the soft tissues were retracted it was found that nature had done a fairly complete exenteration of the mastoid and that, in addition, there was a large sequestrum of the squamous portion of the temporal bone; the postero-superior bony wall of the canal and the superficial cortex of the mastoid, down nearly to the tip, had necrosed and were represented by a mass of dead tissue only; the sequestrum included the temporal ridge and the squama from above and measured 20 mm. square. Between this and the dura was a considerable collection of pus.

We had then a mastoiditis with extensive bone destruction and an extradural abscess, the margins of the abscessed area being completely walled off by inflammatory adhesion of the dura to healthy bone. Cleaning away the visibly diseased tissues, recourse to chisel or gouge being unnecessary, we found that the sigmoid portion of the lateral sinus was exposed as was also the tempero-sphenoidal lobe of the brain above, both on its lateral and under surfaces, the roof of the tympanum and antrum having completely disappeared. The area of exposed dura measured 25 by 35 mm. and it, as well as the sinus, had seemingly resisted the disease. During the investigation the sinus was injured and bled rather freely for a moment but the hemorrhage was promptly controlled by rapidly enlarging the opening in its bony wall, so as to permit the brain pressure from within to close the wound of the soft vessel wall.

It must be remembered that all this exposure of the dura and of lateral sinus, and the destruction of the postero-superior canal wall, the roof of the middle ear and antrum and the

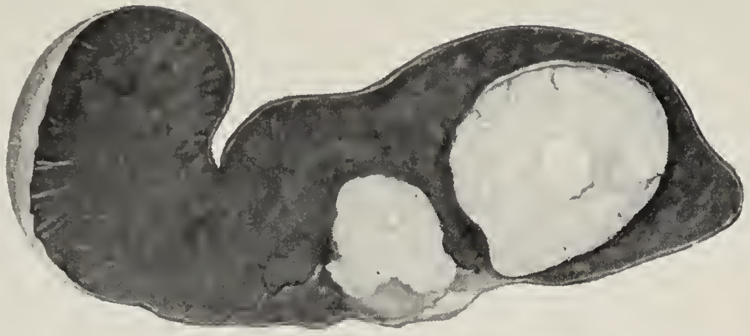

Fig. 1.—Section of spleen showing large areas of caseation.

Fig. 3.—External surface of right hemisphere. Superficial appearance of tubercular areas in the parietal lobe and antero-posterior section through tubercle of the temporal lobe.

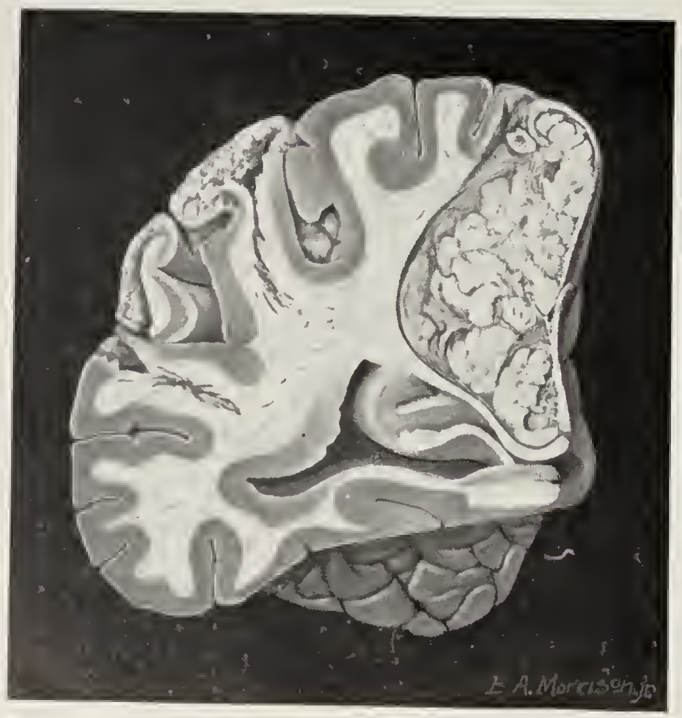

Fig. 4.—Cross-section of the right hemisphere just posterior to the Rolandic fissure. Entire paracentral lobe destroyed. Tubercular destruction of the cortex of the posterior central and parietal convolutions.

Fig. 2.—Base of left hemisphere showing abscess cavity involving almost the entire tempero-sphenoidal lobe.

complete exenteration of the mastoid process, was done by the disease and the operation consisted in doing little more than cleaning away the debris. The wound was lightly packed with sterile gauze from behind the auricle, the area being adjudged too large to attempt closure as in the ordinary so-called "radical" operation, and, because we thought it possible that further exploration of the brain might become necessary.

The immediate result of the operation was most satisfactory. The temperature dropped, with some irregularity, until it reached normal on the third day and there was a steady improvement in the general condition. At first the facial paralysis seemed to be somewhat increased and the child coughed a great deal but, possibly aided by the administration of syrup of the iodide of iron and careful feeding, these symptoms disappeared and he gained rapidly. There were no more convulsions, he began to take an interest in his surroundings, and gradually developed an inclination to use his left arm and leg, so that in the course of a few weeks he could walk and could use the left hand quite freely. The purulent discharge from the aural wound continued to some extent but he seemed to be on the road to complete recovery and on June 2, the local condition had so far improved that an attempt was made to close the post-auricular wound by a plastic operation.

This operation was successfully performed by my associate Dr. J. W. Downey. On June 21 the patient had a sudden rise of temperature to 103.5° F. and for the next ten days ran a mildly septic fever; the cause for this condition we could not determine. On the 1st of August his parents were permitted to take him home with the understanding that he should be brought to the hospital at least once a week for examination: there was still a slight discharge from the ear. He was not well cared for at home, however, and early in October was readmitted to the hospital ward, the ear being in a filthy condition from accumulated purulent secretions and with a fistula due to a partial breaking down of the scar tissue behind the auricle. A thorough cleansing and curettement was performed and he was soon making good progress once more. He had now recovered good use of the arm and leg and we had come to hope that he might be restored to perfect health, although he had occasional unaccountable rises of temperature.

From the 23d of October to the 12th of November his temperature was practically normal and then suddenly rose to 102° F. and he became listless and drowsy. The mastoid wound was reopened and the tempero-sphenoidal region again explored but nothing of importance was disclosed. Dr. John Ruhräh was kind enough to visit the hospital and examine the child for us. He found no evidence of pneumonia, a complication we had thought possible, and could only say that the condition was one of sepsis. At the next dressing of the mastoid wound, the septic temperature having continued, and the child being evidently critically ill, we decided to search the brain for an abscess although there were no clear signs of the existence or localization of such a lesion. A long narrow scalpel was passed into the tempero-sphenoidal lobe in various directions and a grooved director employed likewise, but no pus was obtained. The general condition gradually became worse and the patient died November 26.

An autopsy was performed within a few hours by the resident physician with the following results:

The heart was apparently normal. The lungs, unfortunately, were not as carefully examined as they should have been and for some unaccountable reason were not preserved; they were believed to be normal. The liver, spleen and brain presented very interesting lesions. These organs were preserved in a 5 per cent formalin solution and, later, Dr. Benjamin McCleary, of the College of Physicians and Surgeons, mounted the specimens and made sections for me.

The liver was found to be permeated with vacuoles of varying size, and Dr. McCleary's conclusion that this peculiar condition was probably due to infection by the gas bacillus was confirmed by Prof. William R. Stokes, State Bacteriologist.

The spleen contained two large areas of caseation, typical tubercles (Fig. 1).

The brain was, naturally, in view of the clinical history, the center of attraction and the specimen seems worthy of consideration. The dura was healthy looking, in the main, being but slightly adherent at several small points on the right hemisphere. The left hemisphere (Fig. 2) presented a large abscess cavity involving almost the entire tempero-sphenoidal lobe. The incisions made during operative explorations had passed directly through this cavity but the non-appearance of pus may be accounted for by supposing that the abscess had discharged itself through the middle ear.

The dura was easily stripped away from its points of adherence to the right hemisphere, disclosing yellowish, roughened areas, which, when incised, proved to be solitary tubercles. How extensive these were is well shown in the accompanying illustrations (Figs. 3 and 4). Cutting into the brain substance through the diseased-looking spots on the external surface exposed large areas of tuberculous caseation that involved the greater portion of the temporal and parietal lobes. Figure 3 shows the roughened appearance of the surface, posteriorly, and the deeper condition where an antero-posterior slice was removed from the surface of the temporal lobe. Figure 4 exhibits a cross section of the hemisphere, just posterior to the Rolandic fissure, with considerable destruction of the cortex of the posterior central convolutions, and almost complete destruction of the paracentral lobule on the mesial surface. Sections of these areas of caseation studied under the microscope show them to consist of typical tuberculous tissue.

Review.—It would seem probable that this was originally a case of tuberculous otitis media and that the mastoid disease and the cerebral abscess were direct sequellæ of this infection. It is possible, of course, though difficult to prove with certainty, that the cerebral tuberculosis of the opposite hemisphere was, likewise, the result of infection from the aural focus. The extensive destruction of brain substance in the motor region will explain the early paralysis of the limbs but it is not so clear why there should have been so marked an improvement in function after a mastoid operation of the opposite side. Solitary tubercle of the brain is a very rare condition, especially to such an extent as is observed here. How and why the meninges should have escaped in such a case is a mystery.

ETIOLOGY OF CHRONIC ARTHRITIS.

By Herman W. Marshall, M. D., Boston, Mass.

This subject, chronic arthritis, occurring as a complication of many diseases, cannot be explained in compact, easily comprehensible form; and attempts to simplify it are likely to fail. Moreover, positive proof of its causes is not within reach at present, and not likely to be attained soon, as will be explained later; therefore dependence must be placed upon theoretical statements which endeavor to harmonize pathological conditions with fundamental principles of chemistry, physiology, and bacteriology, and which are justified by improvements in clinical conditions of patients when they are followed in directing treatment. The working hypothesis presented below seems to fulfil these conditions.

Joint symptoms occur in constitutional, infectious and nervous diseases, and their causes are manifold, moreover, the various etiological elements do not act upon a simple tissue but upon a complex structure including bone, cartilage, connective tissue, nerves, synovial membranes, blood capillaries and lymphatics. The result of their action is seen in familiar pathological changes, bone atrophy and hypertrophy, cartilage destruction, periarticular fibrous thickenings and deposits, œdema, intracapsular fringes and synovial membrane changes, ankylosis, joint effusions; also symptoms of pain and stiffness.

Arthritis, therefore, must be conceded to be a complicated process if correct conception is to be obtained of it, and it is well to review the different ways by which joints may be influenced.

Most of the influencing factors may be grouped conveniently as follows:

I. Changes in quality and quantity of blood supply.
II. Disturbances of sensory and trophic nerves.
III. Mechanical factors of pressure and strains due to body weight.
IV. External physical influences, as variations in temperature, traumata, electricity, radiant heat, etc.

Through the blood stream come food materials and products from all body tissues, and occasionally in pathological conditions there are present abnormal products from diseased organs. When colonies of pathogenic bacteria establish themselves there appear in the blood of their host products of their cellular activities as from any group of tissue cells.

The chemical composition of the blood must be considered a highly complex one, due to various food materials, waste products of tissue metabolism, internal secretions, enzymes, pathological elements and toxins; and as the health of joints depends intimately upon the state of the blood, so the problem of joint disease deals with the delicate balance maintained by specially differentiated protoplasm of joint tissues to chemical, nervous, mechanical and thermal stimuli, that such protoplasm is ordinarily subjected to.

Variability in the vital resistance of joint tissues themselves, as well as differences in the various existing stimuli, should also be assumed and is in accordance with variations observed in all living tissues. Definite evidence of abnormalities originating in joints is seen in malignant new growths which occasionally develop there, and perhaps also in hæmophilic joints. The range of such abnormalities seems to be quite wide if clinical evidence be taken as an indication; and their assumed existence makes cases showing extreme pathological changes with very slight apparent causes more readily understood.

The theory, therefore, is proposed that *the causes of chronic arthritis are chemical irritants in the blood, disturbances of the central nervous system, mechanical pressures and strains, and external physical stimuli; and that each etiological factor may be a variable quantity, also that joint tissues themselves have a vital resistance of variable degree.*

Dependence of the Theory upon Clinical Data.

From a few selected patients whose clinical records have suggested probable causes with unusual clearness this hypothesis has been formulated which is of general application. The majority of patients, however, exhibit such confusing and slowly developing joint changes and have such indefinite clinical histories that they have been useless in the past for observation, and reliance has had to be placed only upon favorable instances of quickly developing, severe lesions which have followed and evidently were asscciated with causes equally well marked. When relationships have been once clearly defined then less obvious instances may be better interpreted through principles established in the undoubted ones.

Discussion of the Various Causes of Arthritis.

I. Irritating Substances in the Blood that may cause joint disturbances have the following sources:

a. Chemical products of bacterial growth.
b. Chemical products derived from gastro-intestinal tract.
c. Metabolic products of organ activities.
d. Therapeutic drugs, and poisons like lead.

I (a) Chemical Products of Bacterial Growth are well recognized causes of joint disease and enumeration of different infective foci seems superfluous. Blood examinations have repeatedly shown micro-organisms themselves associated with it. In chronic arthritis generally such examinations are negative, and these processes are due to products brought from a distant focus. In unusually severe, protracted instances bacteria find lodgment in joint tissues and have been demonstrated there exerting their toxic effect more potently.

Pathogenic bacteria produce various chemical substances, and among them toxins and ptomaines are of especial interest in the present connection.

Ptomaines are organic chemical compounds, basic in character, frequently of known composition and stable constitution, that are formed by the action of bacteria upon nitrogenous matter. Some are toxic and others inert.

Ptomaines are mentioned as possible causes of joint disease on account of severe arthritic cases which have recovered promptly after removal of fæcal impactions of the large intestine with enemata. Such patients have large numbers of spore-forming anærobic bacteria in the stools, and these bacteria form substances that are absorbed and appear in the urine; therefore suspicion rests upon excessive development of these comparatively harmless products, and they may be supposed to influence joint structures as the metabolic substances do that deposit sodium bi-urate in cartilage and connective tissue when present in blood in excess. Localization of the origin of arthritis in other cases by evidence furnished from operations upon the bowel help to support this suspicion. Some patients have had severe joint troubles clear up promptly and permanently after colotomies done for ulcerations of the rectum.

Toxins are organic chemical compounds, not generally basic in character, of unknown chemical composition and unstable constitution, that are formed by the action of bacteria upon nitrogenous food materials.

Vaughan and Novy state in their text-book upon Cellular Toxins that "poisons may be produced by the cellular activity of bacteria much in the same way as morphin is formed in the poppy," also that "it is now generally believed that most, if not all, of the pathogenic micro-organisms consist of cell walls containing protoplasm, and that the specific toxin is a constituent of the protoplasm, and that its formation is one of the vital phenomena manifested by the organism in its processes of growth and multiplication. In some species the cell wall is not easily permeable and the toxin is found only within the cell, while in other species the toxin formed within the cell readily passes through the wall and diffuses through the tissues when the germ is multiplying in the animal body."

The chemical nature of bacterial toxins is unknown because they have never been obtained in pure form. From the purest available preparations beliefs have been advanced that they are ferments, and again that they are albuminous bodies, but ignorance of their exact chemical structure must be admitted. That they are synthetic products has been demonstrated in some instances, at least, by cultivation of micro-organisms upon simple food substances from which they were able to elaborate complex toxins in the usual manner.

Gonotoxin is contained within the cell wall of the micro-organism, and filtrates through porcelain from fresh cultures are inactive. The toxin becomes freed only by disintegration of the organism.

Staphylococci form a soluble staphylolysin which acts upon red blood cells, also pyogenetic proteids may be extracted from cell contents of these organisms.

Typhoid bacilli contain within their bodies typhotoxin which is diffused upon disintegration of the bacteria.

Tubercle bacilli produce soluble toxins, and from liquid cultures DeSchweinitz isolated a crystalline body corresponding closely to teraconic acid to which he attributes the necrotic effects observed in tuberculosis. Koch was able to extract from bodies of tubercle bacilli two characteristic bodies belonging to the unsaturated fatty acids. Klebs obtained from them a nuclein, yielding 8% and 9% phosphorus after removal of the above mentioned fats. Glycerine water extracts of bacilli contain a mixture of substances some of which are proteid in character.

Bacteria also form ferments which probably play an important part in the production of morphological changes after the disease process has been inaugurated.

I(b) Chemical Products Derived from the Gastro-Intestinal Tract should be considered the source of irritating substances in the blood, that cause joint lesions in a certain percentage of cases. Clinical evidence of complete recovery from severe arthritis by treatment of well marked intestinal disorders has been the experience of many observers, and the most convincing evidence of this relationship lies in the complete subsidence of arthritic symptoms following colotomies, by which the large intestine is emptied and temporarily put out of function. Complicated conditions exist in the digestive tract owing to presence of multitudes of bacteria which reside there, and live upon the food of their host; therefore for the sake of clearness comparison will be made of chemical changes in food proteids resulting from bacterial activity, and digestion of proteids by tissue cells of the digestive organs.

Through the agency of digestive ferments elaborated in the stomach, intestine and pancreas, food proteids are split into simpler bodies by hydrolytic cleavage. The simple nitrogenous end products are polypeptids, amido bodies, tyrosin, leucin, glutamic acid, a-pyrrolidin carbonic acid, aspartic acid, tryptophan, arginin, lysin and histidin. These comparatively simple substances are absorbed by the intestinal mucosa, enter capillaries of intestinal villi and pass to the liver where further changes occur, and finally appear in the general circulation uniformly as serum albumin, paraglobulin and fibrinogen. Ultimately they are distributed to body tissues by the blood, where they are built up into living protoplasm by intricate metabolic activities of tissue cells. Important changes therefore take place in the intestinal mucosa, liver, and at the cell walls of tissues where ultimate distribution occurs. Waste nitrogenous products enter the blood stream and are eliminated through the kidneys and other excretory organs.

Chemical changes in food proteids resulting from bacterial growth are similar to those observed in digestion as it is carried on by the tissue cells of the alimentary tract. Proteids are split by bacterial ferments into the same simple nitrogenous end products by processes of hydrolysis, but in addition bacteria carry their action further to formation of still simpler bodies. These simple nitrogenous end products of bacterial action are built directly into living protoplasm without mediation of special digestive cells of intestinal mucosa, and liver. Waste products from bacterial vital processes are eliminated directly instead of requiring special excretory organs.

Consequently the protoplasm of bacterial cells must be considered widely divergent from that of tissue cells, as in bacteria are condensed all the vital processes carried on by

stomach, intestine, liver, pancreas, and kidneys; and the metabolic products of bacterial activity must be considered to be distinctly different from products of tissue metabolism. Moreover, upon these differences which cannot be measured at present by existing methods of chemistry and physics, the toxicity of bacterial substances probably depends.

What the exact chemical grouping or physical constitution of substances is that makes them affect joints is not known, nor have all these bodies been identified. It seems certain that bacterial toxins and the antecedents of sodium bi-urate may influence joints, and suspicion rests upon bacterial ptomains and metabolic products from various organ activities.

It is the writer's belief that joint irritants may originate in the digestive tract from excessive numbers of spore-forming anærobic bacteria in the colon, also from tissue cells of stomach and intestine under pathological conditions independently of bacteria, similarly as toxic bodies are known to develop in association with demonstrable pathological states like cancer.

This belief cannot be positively proven, yet rests upon clinical evidence, for there are many arthritic patients whose only illness has been severe chronic dyspepsia, and whose arthritis has improved and grown worse with improvement and relapses of this trouble.

Immunity experiments of introducing foreign substances into the animal body, which lead to the production of protective anti-toxins show that tissues may adapt themselves by forming new substances in their protoplasm, and this remarkable capacity to vary according to requirements of health seems to make the idea more probable that occasional metabolic products are developed in pathological states of gastric and intestinal mucosa, as well as in other organs, that cause arthritis similarly as bacterial toxins produce joint disease. Goldthwait, too, has shown by means of X-rays taken after administration of bismuth subnitrate that arthritis is sometimes associated with displacements of stomach and colon, and that joints improve when abdominal viscera are supported with suitable pads.

This relation of visceral displacements to arthritis may perhaps be assumed to lie in mechanical interference with blood vessels and nerves supplying stomach and intestine, as well as stretching of the tissues, and that the resultant effect is a pathological condition of the lining epithelium of these organs. This pathological state of the epithelium leads to the formation of irritating substances in the blood that affect the joints; and by assuming that joint structures have variable resistances, an explanation can be given why all patients with enteroptosis do not have arthritis.

At present it is impossible to suggest all the pathological states of the digestive tract that lead to production of joint irritants, or to tell what combinations of chemical, nervous, mechanical and physical stimuli act upon the cells of the mucosa to cause their production, but the belief in their existence grows stronger as the number of patients observed grows larger. Whether there are many different substances formed in pathological conditions of the gastric and intestinal mucosa cannot be imagined. The cases that simply have chronic dyspepsia as a probable etiological factor, generally have hypertrophic bone changes which may perhaps indicate a different nature of the irritant from bacterial toxins as the latter lead usually to destructive atrophic changes.

I(c) Metabolic Products from other Organs seem to be the cause of arthritis also, if clinical data be accepted as evidence, and in profound changes going on during pregnancy and at the menopause many observers have noticed development or disappearance of severe joint symptoms. During pregnancy severe arthritis may show marked improvement but it usually recurs again when the uterus has passed through its involution stages. Arthritis may develop soon after pregnancy, and at the menopause, and the most probable explanation is an alteration in the chemical products which these organs supply to the blood. Similar relationships have been recorded between the joints and thyroid, spleen, pancreas and skin, but are less thoroughly established.

That a group of arthritic cases originates in toxic metabolic products of the blood derived from organs must be acknowledged to rest upon scanty data at present, and this paucity of data is due partly to comparative rarity of such disorders. The best established relationships are those of the joints to uterine and thyroid changes. Gout should also be grouped in this large class.

I(d) Therapeutic Drugs used in rheumatic conditions are generally administered to relieve pain. Salicylates circulate in the blood as alkaline salts and exert their effect mainly upon sensory nerves. Urotropin is excreted by synovial membranes as formaldehyde when it is given by mouth and is employed in cases of an infectious nature.

In cases of lead poisoning there are sometimes severe joint pains referable to the action of lead upon nerve cells when it is circulating in the blood.

Ether, circulating in the blood, may produce an unusually prolonged anæsthesia of articular sensory nerves. This fact strongly suggests a pathological condition of them; and indicates possibly the cause of the arthritic processes in such patients. All persons do not respond similarly and only those having very acute attacks exhibit the phenomena strikingly, yet in favorable instances the reaction cannot be mistaken. If a small amount of ether be administered to patients in the manner usually employed in surgical operations, until the patient has lost consciousness and the muscles have just relaxed, there will be upon recovery a sudden diminution of very excruciating pains previously complained of, and such joints exhibit surprising restoration of motion while the anæsthesia lasts. The effect usually lasts a day or so and may terminate the attack. In the few cases observed too profound narcosis or a repetition of it has seemed to cause less favorable results than the first primary anæsthesia, and unfortunately it cannot be generally used therapeutically. However, this property of ether may possibly have diagnostic value in such severe, comparatively rare cases. Discussion of the action of all drugs used in arthritic diseases is too extensive to be undertaken in this paper.

II. The Central Nervous System may have an important influence upon joints, as is well illustrated by destructive joint lesions occurring in tabes dorsalis and syringomyelia; and if clinical appearances are to be credited there are numerous attacks of arthritis which are initiated by nervous disturbances, and it should be remembered that nerve cells are subject to variations like all other tissues and are dependent upon the same variable states of the blood. An unusually sensitive nervous system acting upon joints of abnormally low resistance may be supposed to occur occasionally, and will account for some progressive cases which obstinately grow worse in spite of treatment.

In such individuals mental strain or prolonged worries destroy their nervous balance and the joints suddenly become affected. This action may not be a simple one in every case, for it should be remembered that all organs are under control of the nervous system, and that simultaneously there may be initiated digestive disorders together with joint troubles; certainly such cases are met with in practice which exhibit nervous symptoms, indigestion and arthritis.

The question arises in such instances, which is the cause and which the effect, because it is known that digestive products influence all tissues, including nerve cells, and that nervous stimuli undoubtedly affect digestive functions. It seems reasonable to suppose, and it is borne out by clinical histories, that sometimes one, and sometimes the other cause starts the trouble according to the relative vital resistance of nerve and digestive cells.

The nervous system accordingly may be supposed to influence joints directly through articular nerves or indirectly through other organs by setting up abnormal processes in them which result in irritants in the blood.

Pain in arthritic diseases may come from pressure upon nerves as they emerge through vertebral foramina and is then referred to regions irrespective of joints. Dull aches in joints sometimes are due to pressure upon terminal filaments of sensory nerves, yet perhaps in the majority of cases accompanied by incessant grumbling pains they express an underlying pathological process going on in the nerve cells which are abnormally weak, or which are being subjected to chemical irritants in the blood.

III. Mechanical Irritation to Joints from pressure of body weight, occupation strains, and traumata are important and well recognized, and there are always factors of weight and motion to be considered regardless of the original causes, which may aggravate or perpetuate joint lesions after the initial cause has ceased to act.

Mechanical pinching of inflamed synovial membranes frequently results in the hypertrophied villi seen so commonly in operations. The pressure of body weight may continue arthritic processes associated with deformity simply by abnormal strains upon the affected joint structures; and there are so many cases of arthritis developing after traumata that no reasonable doubt can exist that this mechanical factor initiates the process in some instances.

IV. Various External Physical Agencies have been repeatedly recognized as etiological factors by clinicians; workmen who are subjected to extreme and rapid changes of temperature in foundries are supposed to be more likely to rheumatic affections; and women whose occupation requires continual irritation of hands from scrubbing or dipping into water frequently develop arthritis confined to these members. Probably in many such instances there is a true relationship between external causes and arthritic disease, at least in patients who have in their blood toxic substances likely to attack points of weakened resistance.

Application of the Theory to Treatment.

Many patients have been improved, and some of them have been completely cured of severe arthritis by keeping in mind the various etiological factors that have been enumerated; consequently this theoretical conception has proven to be of very practical value.

Treatment should consist in a search for the most probable underlying causes rather than in attempting to treat many possible origins in the same individual; moreover recognition that several causes often act together simultaneously, permits a better comprehension of the complicated conditions that frequently are observed.

Compulsory sedentary life of patients with severe joint disease tends to produce digestive disturbances and constipation with formation of irritating substances in stomach and intestine; and these may get into the circulation and prolong irritation in weakened joints after original causes have ceased to act. The importance of the digestive tract becomes obvious when consideration is given to the frequency of its disorders, and to the fact that its regulation is an important way of influencing the health of all tissues independently of any direct connection between it and joints. Simple modifications of diet, stomach washings, normal saline enemata, and supporting pads for relaxed abdominal walls have already been productive of very great benefit to arthritic conditions in selected cases.

Local therapeutic measures should be carried out thoughtfully; for example, immobilization of joints by plaster casts may cause rapid subsidence of symptoms and return of normal conditions in inflamed joints when the cause is mainly due to the mechanical irritation of motion and body weight; while in cases in which the origin lies in toxic substances of the blood such a procedure may permit the inflamed synovial surfaces to become adherent, and the joints to stiffen.

Thermal measures, as hot applications or bakings increase circulation locally and stimulate the protoplasm of cells. This may be beneficial in some instances, but when joint tissues are struggling with toxins in the blood that tax their resistance to the utmost, over-stimulation of the worn-out tissues is likely to happen, with a worse result finally than if these therapeutic measures had not been used. Such treatments should be mild at first and discontinued soon if no amelioration takes place, or continued cautiously only as long as symptoms improve.

It is only possible to suggest in this article how applications

of the working hypothesis which has been presented may yield an increased number of cures through careful consideration of each individual case instead of employing routine measures and drugs without thought of etiology of the disease.

Accordingly this working plan, although not fully established, seems the best method of treatment available at present, and it will probably be modified and elaborated as data are assembled from cases in which it has been applied. It has already proven useful, and, therefore, perhaps may be of sufficient general interest to warrant publication.

NOTES ON NEW BOOKS.

A Text-Book of Diseases of the Ear. By Macleod Yearsley, F. R. C. S. (*Chicago: Chicago Medical Book Co., 1908.*)

We recommend this work as one of the best written in the English language on this subject. It is simply and clearly written so that the beginner in otology can easily follow it and so comprehensive that the special worker in this field can learn much from it.

All of the chapters are so well written that it is impossible to praise one more than another. However, the author is to be congratulated for his additions to the usual routine chapters, namely, those on the influence of general diseases of the ear, aural reflexes, deafmutism and medico-legal and life insurance.

In discussing the surgical treatment of the contra-cranial complications of middle ear suppurations, the author lays stress on the foolishness of approaching these conditions, as so many surgeons do, by inaccurate trephining. The proper method is to lay bare the original seat of the disease in the middle ear or mastoid and follow the extension to the brain as can usually be done.

Throughout the book are many references, which though not exhaustive are very useful and interesting, in that they indicate the historical development of the subjects discussed.

Numerous original illustrations help to make clearer the various diseases and operations described.

Sylvan Rosenheim.

The Pathology of the Living and Other Essays. By B. G. A. Moynehan, M. S. (Lond.), F. R. C. S. Price, $2.00. (*Philadelphia and London: W. B. Saunders Company, 1910.*)

Those who have not read Mr. Moynehan's papers as they have appeared in the British Medical Journal and elsewhere will be glad to secure them in this form; and all students of surgery will find them well worth reading. In these essays the author presents the gist of his wide surgical experience, which, along the line of gastro-intestinal operations, has been surpassed by but few. He is a keen observer, of sound judgment, and his knowledge of the subjects he deals with so thorough that this small volume contains much more of real value than many larger volumes dealing with the same subjects.

The Expectation of Life of the Consumptive after Sanatorium Treatment. By Noel Dean Bardswell, M. D., M. R. C. P., F. R. S. (Ed.), etc. Price, $1.50. (*Edinburgh, Glasgow and London: Henry Frowde and Hodder & Stoughton, 1910.*) *Oxford Medical Publications.*

The author's work is well known to and appreciated by all students of the problems of tuberculosis, and his latest volume is one of exceptional interest, as such statistics as he furnishes are very scarce. Dr. Bardswell has followed his patients with care and diligence so that his figures are of more than ordinary value. After a brief introduction he describes the "Method of Classification Adopted," which conforms with that of the National Association for the Study and Prevention of Tuberculosis, and then gives a "Summary of Results of Treatment." This he follows with a "Commentary," and then concludes with "Life Histories" of patients under his care who had either "incipient," "moderately" or "far advanced" disease. Hardly any book on the clinical side of tuberculosis that has lately appeared has the importance of this study, which is admirably presented.

Consumption: Its Prevention and Home Treatment. A Guide for the Use of Patients. By H. Hyslop Thomson, M. D. Price, $1.00. (*London: Henry Frowde and Hodder & Stoughton, 1910.*) *Oxford Medical Publications.*

This small guide is a practical one and may be cordially recommended. In ten brief chapters the author discusses clearly The Causes of Consumption, How to Avoid Susceptibility, Precautions against Infection, The Necessity for Home Treatment, Requirements for Home Treatment, The Temperature and Body Weight, Personal Measures, The Importance of Routine in Treatment, The Diet of the Consumptive, and When to Seek Medical Advice.

Manual of Surgery. By Alexis Thomsen, F. R. C. S., Ed., and Alexander Miles, F. R. C. S., Ed. Two volumes. 3d edition revised and enlarged. Price $7.00. (*Edinburgh, Glasgow and London: Henry Frowde and Hodder & Stoughton, 1909.*) *Oxford Medical Publications.*

This book was reviewed in this journal in July, 1908, and there is only to be added that the authors have revised the sections on syphilis, serum and vaccine treatment, the surgery of individual nerves, the use of the Röntgen rays in the diagnosis of certain rare affections, etc. The first volume is devoted to general surgery, the second to regional surgery. The illustrations are plentiful, but not of fine quality. The print and paper are good and the volumes are of a comfortable size. The work is one of many useful surgeries, of which there is a superabundance, for medical students.

Burdett's Hospitals and Charities, 1910. The Year Book of Philanthropy and Hospital Annual. Twenty-first Year. Price, 10s. 6d. (*London: The Scientific Press Limited.*)

Each volume adds to the importance of this publication, to whose value attention has been frequently drawn. The immense amounts of carefully detailed statistics in regard to hospital, and other charity institutional expenses cannot be found in any other work. Comparison with expense accounts of American hospitals is almost out of the question, but all superintendents may learn much from a study of the reports furnished by Sir Henry Burdett. We wish that the trustees of the Russell Sage fund might see their way to publish a similar work for the United States.

U. S. Department of Agriculture, Bureau of Animal Industry.—Circular 153. (*Washington: Government Printing Office, 1910.*)

This circular on "The Dissemination of Disease by Dairy Products, and Methods for Prevention" has been well prepared. It is made up of five chapters, as follows: 1, Milk as a Carrier of Contagious Disease, and the Desirability of Pasteurization, by G. Lloyd Magruder; 2, The Importance of a Wholesome Milk Supply by John R. Mohler; 3, The Relation of the Tuberculous Cow to Public Health, by E. C. Schroeder; 4, Interpretation of Results of

Bacteriological Examination of Milk, by L. A. Rogers and S. H. Ayres; and 5, Pasteurization, Its Advantages and Disadvantages, by M. J. Rosenau. The papers, although brief, are concise, and set forth in a plain style matters of importance to all consumers of milk. These educational pamphlets issued by the different bureaus in Washington are one of the most valuable products of our government, and the work coming from the Bureau of Animal Industry deserves special commendation. We would urge all medical men to secure and study these reports which deal with the social welfare of the country at large.

Text-book of Hygiene. By George H. Rohé, M. D., and Albert Robin, M. D., etc. Fourth Revised and Enlarged Edition. Illustrated. (*Philadelphia: F. A. Davis Company, 1908.*)

The last edition of Rohé's Hygiene, edited by A. Robin, presents a number of interesting changes which make it more acceptable as a text-book for students and as a reference book for physicians. The subject material has been rewritten, mostly by well-known authorities in the various branches. Thus, Surgeon-General Walter Wyman has revised the chapter on Quarantine, Surgeon-Major McCaw, the one on Military and Camp Hygiene; Surgeon-Major Beyer, the one on Naval Hygiene, while Dr. Frances W. Upshur has edited the chapters on School Hygiene, Exercise, and Training, etc. Attention should be particularly directed to the section on Naval Hygiene, by Dr. Beyer. It is one of the best chapters in the book and one of the best small treatises on the subject of Naval Hygiene extant. The bacteriology of this book is much to be criticised. The information given is antiquated and even if it were up to date would be totally inadequate to the subject. In the analysis of water, for instance, slightly over two pages are given up to the bacteriological examination, while about ten pages are devoted to the chemical tests. Yet the bacteriological findings are admittedly more delicate and trustworthy than the chemical and will more certainly reveal a sewage pollution. Despite this fault, which runs through the whole book, it is a valuable and interesting volume on hygiene and should prove useful to sanitarians as well as to medical men. The value of the book would be much enhanced if the present editor would eliminate the foolish questions addressed to the reader at the end of each chapter. They create a superficial resemblance to a "quiz-compend" and have no place in so well written and scientific a book as the present edition.

Intestinal Auto-Intoxication. By A. Combe, M. D. Together with an Appendix on the Lactic Ferments with Reference to Their Application in Intestinal Therapeutics. By A. Fournier. English adaptation by William Gaynor States, M. D. (*New York: Rebman Company, 1908.*)

In this work the author has presented in a very readable and instructive manner the diversified subject of intestinal auto-intoxication. His treatment of the subject is comprehensive and distinguished for the clear manner in which the various subdivisions are laid before the reader. The knowledge of the chemical processes which take place in the intestinal tract which is so necessary for the reader in order that he may clearly interpret the pathological physiology of intestinal auto-intoxication is briefly and well presented. Perhaps this feature of the work is the best.

A very interesting chapter is that dealing with the antitoxic functions of the body, in which are discussed:

1. The factors limiting intestinal putrefaction.
2. The triple line of defense surrounding the intestine, *i. e.*, the intestinal mucosa, the liver, and the antitoxic glands.
3. The elimination of intestinal poisonings.

Other instructive chapters are those dealing with the experimental pathology, diagnosis, and the symptomology.

A very large part of the work is devoted to the treatment of intestinal disorders, and here the author has helped the reader very greatly by organizing into a schema the rather confused knowledge that has grown up with the development of this special side of the subject. The discussion of the divisions of nitrogenous intestinal putrefaction, lactic ferments, the physiology and classification of yeasts contains much information of value. The volume is brought to a close with a chapter on stimulating the action of the antitoxic glands and the emunctories of the body, that is, the renal, cutaneous and intestinal emunctories.

The author acknowledges his use of the classical works of Strauss, Albu v. Jacksch, Charrin and Widal in his preface. This volume is an instructive and simple presentation of a rather complex subject, and has the especial merit of bringing into one work information that has been heretofore largely scattered through the literature.

Protozoölogy. By Gary N. Calkins, Ph. D. Illustrated. (*New York and Philadelphia: Lea & Febiger, 1909.*)

The recent edition of Protozoölogy by Gary N. Calkins, Professor of Protozoölogy in Columbia University, New York, may be recommended not only to students of biology, who have a special interest in the study of the unicellular organisms but also to students of medicine, who are anxious to learn the relation of these organisms to disease in man and in the lower animals.

The book is based on the author's lectures on this subject in the Lowell Institute during the fall and winter of 1907. It is divided into 10 chapters illustrated with engravings and colored plates. The first chapter is devoted to morphology and classification, the second to physiology, the third to the life cycle, the fourth to conjugation, maturation, and fertilization, etc. In these chapters the author gives us a succinct account of the general principles, of forms, structure and function underlying our knowledge of the protozoan organisms. From the fifth chapter devoted to parasitism, on, through the concluding sections, the essentially medical side of the science is emphasized, and its bearing on the cancer problem and on such diseases as syphilis, small-pox, and scarlet fever is thoroughly reviewed. Both the Spirochaetae and the Trypanosomes are considered at length, and the method of transmission of protozoan diseases by insects is well presented. In the last chapter devoted to the pathogenic Rhizopoda, the etiology of dysentery, small-pox and rabies is treated of at some length, and the author presents the evidence in favor of the view which he possibly more than any other protozoölogist maintains; namely, that the Negri bodies stand in etiological relationship to rabies and the bodies described by Councilman in small-pox in the same position in regard to this disease. At the present time, possibly, this view is not entirely in harmony with the views of many protozoölogists nor with the views of the cytologists who are apt to look upon the various structures described in these affections as degeneration products or cell inclusions, which are not themselves the parasite, but may possibly harbor it.

Prof. Calkin's book is an excellent defense of the contrary opinion that these structures form in reality part of the life cycle of a protozoan organism, and on this account it deserves an especial study by medical men. It can be particularly recommended to those physicians who are apt to come in contact with the various infectious diseases of unknown origin, especially those seen in the tropics.

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CONTENTS.

FATAL APNŒA AND THE SHOCK PROBLEM.[1]

By Yandell Henderson, Ph. D.,

Assistant Professor of Physiology in the Yale Medical School.

The topic upon which I shall speak is a very old one, perhaps the oldest in medicine. Yet I shall ask you to regard it from a somewhat novel standpoint. At the present time it is very easy to find novel treatments of old topics in physiology. It is not necessary to discover new material. One need only look at the data of normal physiology from the standpoint of the abnormal. With little labor on his own part the abnormal physiologist of to-day may draw dividends upon the capital accumulated by the normal physiologist in the past, especially in that field to which I shall invite your attention this evening.

This field of physiology is comparable to one of those mines in Austria from which came ore yielding uranium. For many years only the uranium was extracted and the residue of the ore after this extraction was thrown upon the waste heap. At last it was discovered that this waste was rich in radium and the heaps of material hitherto worthless became again immediately of great value. So it is in my topic. Physiologists in the past have dug out of the depths immense amounts of material. From this they have extracted theories and explanations of the normal, but they have quite generally neglected to work out those elements which would be of practical usefulness. They have, I fear, been even a little scornful of those who have descended from the heights and have offered their material as useful to the clinician. That which I shall attempt consists merely in extracting some principles of abnormal function and, as I hope, of practical and applicable clinical usefulness from the heaps of material accumulated by previous physiologists.

During the past hundred years an immense amount of work has been done in the field of respiration. From this material numerous investigators have extracted every particle of in-

[1] Read before the Johns Hopkins Hospital Medical Society, December 6, 1909.

formation bearing upon the problem—How and why do we breathe? I have attempted to extract from this same material the answer to the question—How and why do we stop breathing? As every one of us will some day stop breathing, even a partial answer to the latter question appears well worth extracting.

The simplest and clearest cases of fatal apnœa are those which occur after intense pain. In order to bring my particular problem clearly before you, I will instance a case. A man in the prime of life was setting off fireworks on the evening of the last Fourth of July when a giant firecracker exploded in his hand and shattered it. There was no considerable loss of blood. For two hours he suffered intensely, although he received a quarter of a grain of morphin. Then anæsthesia with ether was attempted, and his breathing immediately began to fail. The anæsthetic was withdrawn, and respiration improved. Three hours after the accident he stopped breathing quite suddenly. Artificial respiration and stimulants were ineffective, and he died. Yet his pulse was fairly good before and even for some minutes after respiration ceased. Why did that man die? [2] In order to make the further discussion of my topic clear I will present immediately the explanation to which, as it seems to me, all the data point. During the period after the accident his breathing was of the type which insupportable pain always excites. This hyperpnœa involved a far greater ventilation of the lungs than normal breathing affords. Consequently the CO_2 content of the blood, and finally also of the body as a whole, was greatly diminished. When anæsthesia was attempted it was almost inevitable that respiration should show signs of failure. CO_2 is the normal stimulant of respiration; therefore, after this normal chemical stimulant to breathing had been reduced, pain alone maintained the breathing. Anæsthesia removed the pain. Finally breathing stopped for the very simple reason that there was not enough CO_2 left in the blood to excite the respiratory center to activity. To this condition of diminished CO_2 content in the blood Mosso has given the name "acapnia" from the Greek "kapnos," smoke. Literally, acapnia means smokelessness. Perhaps I should remind you that the arterial blood normally contains 20 volumes per cent of oxygen, and 40 of CO_2; and that the body as a whole has an enormously greater store of CO_2 than of oxygen.

Before I proceed to explain the experimental basis for this long range diagnosis, I wish briefly to consider the question whether this was a case of surgical shock. The condition to which the surgeons apply this name has been defined by Crile as consisting essentially in a low arterial pressure. Early in my investigations upon traumatic shock I was met by an unexpected difficulty. At first I tried to produce shock as Crile had done by exposure and irritation of the abdominal viscera. To my surprise, the dogs upon which I worked usually died of failure of respiration long before arterial pressure had fallen to such an abnormally low level as would accord with Crile's definition. All modern work upon shock must take its starting point from the investigations of Crile, splendid as they are in extent and thoroughness. Accordingly, I reread Crile's work with this point in mind, and I found that his experience had been precisely the same as my own. Crile says that "in 103 of the experiments in which the exact manner of death was recorded, or in which in the course of the experiments the heart or respiration failed first, respiration alone failed in 90, the heart alone in 4, and both simultaneously in 9. In many instances the heart was beating strongly and the blood pressure was fair at the time respiration failed." In many of Crile's experiments he was obliged to employ artificial respiration in order to keep his animals alive until the low blood pressure developed. Otherwise, as this quotation shows, nearly all of his animals would have died of failure of respiration. I do not desire to alter Crile's definition of surgical shock as "low blood pressure." I would apply the name "fatal apnœa vera" to the death of the man of whom I spoke, and to the failure of respiration observed by Crile in the dogs of his experiments and in the animals employed in my own. All that I contend is this: After intense pain, but in the absence of hemorrhage, death usually results from failure of respiration before arterial pressure has fallen to a dangerous level. Under experimental conditions it is really difficult to induce a condition meeting Crile's definition. It is necessary that the subject should be watched very carefully and that every time respiration begins to fail some afferent nerve should be irritated so vigorously, that apnœa is prevented, and the respiratory center is forced into renewed activity. By conforming with this precaution, however, I have succeeded in inducing typical surgical shock in some 20 animals. It was my good fortune to have Dr. Crile as a witness of one of them, so that when I use the term "Surgical Shock," I mean the real thing—the shock of Crile.

I shall not attempt in the brief time at my disposal to analyze in detail this condition of low arterial pressure. I may say, however, that I do not believe it is due to fatigue or inhibition or failure of any sort in the vasomotor center. On the contrary, that center does its full duty almost to the last. It is like the Roman legionary at the gate of Pompeii, who stood at his post until overwhelmed by the ashes of Vesuvius. In less figurative language the fact is that the small arteries are contracted, not relaxed, during the stage of low arterial pressure, as Malcolm in England, and Seelig and Lyon in this country have shown. The failure of the circulation appears rather to be due to diminution in the volume of the blood by transudation of its fluid out of the vessels into the tissues, a process like edema. It is a complex peripheral process induced initially by the influence of acapnia upon the veins and capillaries and upon the tissues. Thus when death follows intense physical suffering, not complicated by hemorrhage, there are two principal stages. At first, the excessive breathing diminishes the CO_2 content of the blood. If at any time after this condition of acapnia has been induced the pain is greatly diminished and the respiratory center is thus allowed to relapse into a standstill, fatal apnœa vera may occur. If, on

[2] It has been suggested to me that the "toxins of roasted tissue" were a factor in the case. On the contrary, however, the burns inflicted were very slight.

the other hand, the pain is sufficiently continuous to keep the respiratory center continually excited then apnœa is prevented, and the condition of acapnia becomes more and more acute and general until the circulation fails, and the subject sinks into surgical shock according to Crile's definition. Both fatal apnœa and the more slowly developing failure of the circulation are due initially to acapnia induced by the excessive breathing occurring under torture.

So much for the point of view of an advocate of the acapnial hypothesis of surgical shock. It will next be necessary for me to attempt to show you how these somewhat heterodox views can be derived quite logically, I believe, from the orthodox doctrines of normal physiology.

The textbooks used to tell us that there were four factors involved in the maintenance of normal breathing. First, an automaticity of the respiratory center similar to that of the heart;[3] second, afferent nerve influences, especially those induced through the vagi from their sensory endings in the lungs; third, the need for oxygen; fourth, the excess of CO_2 in the blood.

The first of these factors has been proved by the investigations of the last ten years to be non-existent. A perfectly normal center, such as mine now is, will come to a standstill the instant it ceases to be driven. It is so pitilessly lazy that it will let its owner die if it is not whipped or spurred into a renewal of activity. The respiratory center, therefore, is not automatic in the sense that it will run of itself.

On the second factor it has become increasingly evident that, although the center is responsive to afferent nervous impulses, it is thus influenced only in the same manner as a clock is influenced by the length of its pendulum. The force corresponding to the spring or weight in a clock is afforded by chemical conditions in the blood. Variations in afferent impulses reaching the respiratory center induce alterations in the form of breathing, especially in its rate, as the pendulum regulates the ticking of a clock, but they have little influence, under ordinary conditions, upon the total pulmonary ventilation. Thus to take an illustration, in myself at the present time my respiratory center, in inducing the sounds which you hear, is subject to a flow of nervous stimulations. Yet the total rate at which my lungs are being ventilated is not thereby altered from the rate at which they would be ventilated were I not speaking. The ticking of my respiratory clock is different under the two conditions, but the rate at which the weight falls or the spring unwinds, or in other words, the rate at which CO_2 is eliminated, is dependent upon the respiratory needs of my body.

Perhaps there is no idea more firmly fixed in the medical mind, or which it will be harder to root out, than the idea that the respiratory center is sensitive to alterations in its oxygen supply. Yet during the past few years it has been conclusively demonstrated that within wide limits the respiratory center is wholly indifferent both to excess and to lack of oxygen. It should be added, however, that this statement needs modification so as to admit that conditions which result from anoxhæmia do irritate the center. These conditions, however, are produced slowly and in the tissues, not primarily in the center. Even to a total lack of oxygen the respiratory center makes no immediate response, although it may be killed thereby. Thirty years ago that brilliant Swiss investigator, Miescher, expressed the essential truth regarding the regulation of normal breathing in these words: "Over the oxygen supply of the body CO_2 spreads its protecting wings." The form of death from respiratory failure of which I have been speaking is very simply explained as due to the withdrawal of these "protecting wings." After they are withdrawn death ensues from lack of oxygen.

The crucial experiment in this field is that of voluntary forced breathing. The experiment is so simple and so easily performed at any time by anyone that it ought to become universally familiar. It is only necessary to breathe as rapidly and as deeply as you can, taking care that you do not inspire with the diaphragm while expiring with the costal muscles. Keep this up for one or two minutes, or if you have the courage, for five or ten minutes. Thereby you will induce in yourself a moderate degree of acapnia. When you cease the voluntary effort you may find that your hands are temporarily paralyzed. Your legs and arms may be asleep. You may shiver as in a chill. You will feel strangely lightheaded. Breathing exercises are no new thing. They have been practiced for three thousand years by the Buddhist monks of India. Some of those American cranks who have taken up the so-called Yoga philosophy and practice breathing exercises attain such a degree of mental exaltation and light-headedness after forced breathing that they feel themselves literally lifted from the ground and floating in the air. I have never myself quite left the floor, but once or twice I have felt as if I were going to. The main point in performing this experiment, however, is this: If your efforts have been sufficiently energetic and a considerable degree of acapnia has been induced, when you stop forcing yourself to breathe, you will stop breathing altogether. In this respect the respiratory center is entirely automatic. If you have previously reduced your store of CO_2 sufficiently, you will remain breathless and without any desire to breathe, until you turn blue in the face. It is not at all improbable that a man could thus commit suicide.

This form of respiratory failure is termed apnœa vera, or true apnœa. That acapnia is the cause of apnœa vera has been demonstrated by Haldane and Priestley. They have shown that it is quite easy to catch the last of the air expired in a deep expiration, and that this air is the alveolar air of the lungs. Upon themselves and others they have performed a long series of analyses of the alveolar air. They find its composition in respect to the CO_2 tension to be extraordinarily constant. In the depths of a Welsh mine or on the summit of a mountain, with a variation in atmospheric pressure of several hundred millimeters of mercury, the respiratory center automatically maintains the alveolar tension of CO_2 constant to within a fraction of 1 per cent. On the other hand, under these varying conditions the oxygen tension in the lungs varied

[3] Foster, M.: A Text-Book of Physiology, 1895, pp. 371-2.

by more than one-third without the activity of the respiratory center being thereby in the least degree modified. When a man breathes pure oxygen Haldane has shown that his respiration continues to be controlled solely in relation to the CO_2 elimination. The addition of 0.2 per cent CO_2 to the air automatically doubles a man's pulmonary ventilation.

Recently Haldane and Poulton offered a demonstration before the British Physiological Society in which Poulton performed forced breathing for two and a half minutes. Then he lapsed into apnœa. After a couple of minutes his face assumed a leaden corpse-like appearance characteristic of great anoxhæmia. Yet it was a full minute after this before he experienced any desire to breathe. Several of the British physiologists in the audience were so upset by the spectacle that they could scarcely be hindered from performing artificial respiration upon him. One or two were obliged to leave the room.

Such experiments as these, and they have been repeated sufficiently often to assure their correctness, demonstrate conclusively that lack of oxygen itself is not a stimulant to the respiratory center. After the oxygen supply of the blood, lungs, and tissues has been exhausted,—and this in such a case as that of Poulton appears to occur in two or three minutes,—the asphyxia of the tissues results in the appearance in the blood of the products of incomplete tissue combustion. This is a form of acidosis. The acidosis bodies stimulate the respiratory center, or rather add their stimulating influence to that of the CO_2 remaining in the blood. Thus, after a short period of forced breathing, apnœa lasts until the CO_2 has reaccumulated in the blood up to the normal amount—that is up to the threshold stimulating value for the respiratory center. But after more prolonged forced breathing and apnœa lasting until acidosis results, the breathing recommences while the CO_2 content of the blood is still below normal. In experiments of this character Haldane and Douglas have found a beautiful explanation of Cheyne-Stokes breathing. A man after prolonged apnœa starts to breathe because of the combined influence of the acidosis bodies and of the CO_2 remaining in his blood. The first few breaths, or even the first breath, supplies sufficient oxygen to oxidize the acidosis substances; and the subject lapses into apnœa. The repetition of this cycle affords typical Cheyne-Stokes breathing in a perfectly normal man.

The influence of acidosis in shortening apnœa, and thus preventing death from asphyxia, is illustrated by an experiment by Vernon. He finds that without forced breathing he can hold his breath for less than a minute. After forced breathing he can hold it three or four minutes. After forced breathing ending with two or three inhalations of oxygen he has held it for eight minutes and thirteen seconds. This is at present the record, and one which I personally have no desire to beat.

The experiments of my collaborators and myself in this field are in part already in print, in part they are now in the hands of the printer, and the remainder will appear within a couple of years. I will not, therefore, burden you with their details, but I will briefly run over their essential points. In one series of experiments the thorax of the dogs on which we worked was opened and the animals were maintained under artificial respiration. The operation was so severe that if trauma or irritation of afferent nerves in and of itself were the cause of shock all of the animals should have passed rapidly into this condition. It was found, however, that actually the sole condition determining the rate at which the animals sank into shock was the pulmonary ventilation. If we did not give them too much air, the circulation was maintained at a normal pressure for many hours. If, on the other hand, the pump with which artificial respiration was supplied was worked a little too vigorously, the animals sank rapidly into shock. Thus excessive artificial respiration affords a means of inducing a condition closely similar to, if not identical with, that induced by pain.

In another series of experiments the abdominal viscera were exposed, handled and aerated. This, of course, induced continuous hyperpnœa. I should say parenthetically that all of the animals in these experiments were anæsthetized or otherwise drugged to the point of complete unconsciousness. It is not the consciousness of pain, but the effect of pain (*i. e.*, intense afferent irritation) upon the respiratory center which induces acapnia and shock. In these particular experiments in which the abdominal viscera were thus treated both the arterial and the venous blood were analyzed for their gases. It was found that the development of shock fell into two stages. At first, the CO_2 content of the arterial blood diminished gradually, the oxygen content remaining unaltered. During this process the oxygen content of the venous blood steadily diminished until finally the blood in the large veins was totally deficient in oxygen. When this stage was reached the tissues did not receive enough oxygen to meet their respiratory needs. If irritation of the viscera was stopped prior to this complete venous anoxhæmia, fatal apnœa occurred. After this time fatal apnœa was less likely to occur, but the volume of the blood stream appeared to diminish steadily. This, as I have already suggested, I believe to be due to the alteration in the respiration of the tissues, to the development of tissue asphyxia and of acidosis, and to the consequent transudation of the fluid of the blood into the tissues. I believe that this process is one of imbibition or absorption of water by the colloids of the protoplasm of the tissue cells,—a process similar to the swelling of fibrin in dilute acids. The details of this process, however, still require a great deal of work for their complete elucidation.

In two other sets of experiments we have attempted to compare the effects of excessive artificial respiration with the effects of intense afferent irritation. Their object was to see to what extent the after-effects of trauma are due to the acapnia resulting from the hyperpnœa. For the former we used two large automobile tire pumps, one of which forced air into the lungs while the other withdrew it. When a dog is subjected to this treatment for 20 or 30 minutes and then left to himself, he lies perfectly quiet without attempting spontaneous breathing for many minutes. In the more successful experi-

ments the subjects have lain perfectly quiet until in eight minutes their hearts failed for lack of oxygen.

In the other and comparable set of experiments the animals were forced to supply their own excessive pulmonary ventilation. The sciatic nerves were dissected out and stimulated for 20 to 30 minutes. Thereby a vigorous natural hyperpnœa was maintained. When the stimulation was discontinued the animals ceased to breathe altogether and in the more successful cases lay perfectly quiet until after eight minutes when their hearts failed for lack of oxygen. The two sets of experiments have afforded results so nearly concordant that it is difficult to distinguish between them. Apparently in these cases at least all of the after effects of pain are explicable as due to the acapnia which pain (*i. e.*, the breathing of pain) induces. Apparently if Torquemada had administered the tortures of the Spanish Inquisition in an atmosphere of 5 or 6 per cent of CO_2, while the sufferings of his victims would not have been less, they would not have developed surgical shock. Certainly thereafter they would not have died of fatal apnœa.

Those cases of fatal apnœa which more than any other interest the clinician are, I suppose, the failures of respiration under anæsthesia. If the patient ceases to breathe in his bed it is his own fault, but if he does so on the operating table the anæsthetist has to bear the responsibility. For such cases of apnœa the acapnia hypothesis affords a simple explanation. Anæsthesia diminishes the strength of inflowing afferent irritations. Furthermore profound anæsthesia raises the threshold of the respiratory center for CO_2. In other words, the respiratory center of a man or animal in profound anæsthesia automatically maintains more than the normal CO_2 content in the blood. Thus when a man or woman or child has suffered prolonged pain and thereby has been brought into a condition of more or less acapnia, the production of anæsthesia by removing the afferent pain stimuli, and also by raising the threshold, that is by diminishing the sensitiveness, of the respiratory center for CO_2 inevitably leads to apnœa.

This, however, is not quite the whole story. When I first tried to produce fatal apnœa I kept the dogs upon which I worked under ether alone without morphin. The experiments failed. Either the animals exhibited no apnœa or only a very brief period of respiratory standstill. In some cases after prolonged artificial respiration or intense stimulation of afferent nerves, although a considerable degree of acapnia had been induced, the subjects continued to breathe and even to breathe excessively. After a great deal of trouble it has finally appeared that this was due to nothing more nor less than the well-known influence of ether as a respiratory stimulant. As a rule dogs are quite prone to that peculiar phase of anæsthesia called "ether excitement." In this condition we find that the respiratory center will spontaneously and without afferent irritation maintain a hyperpnœa sufficiently vigorous to produce acapnia.

In this connection I remember one of my bitterest disappointments. A fine strong dog of irritable temper had been given me by a friend for an experiment in which acapnia was the last thing wanted. I attempted to bring the dog under ether. He fought, breathed violently, came part way under the influence of the anæsthetic, and then out again. Finally I succeeded in getting him quiet, and immediately he stopped breathing. My utmost efforts failed to induce him to breathe again. This was before I knew that an animal can breathe too much. Nothing whatever had been done to this animal except to induce acapnia by means of ether excitement, and then to induce apnœa by restoring the threshold of the respiratory center to its normal level by full anæsthesia.

Now a few words on prophylaxis. The acapnia hypothesis requires the prevention of excessive pulmonary ventilation. The administration of morphin and full anæsthesia diminish the activity of respiration under pain and thus prevent acapnia. If, however, you administer morphin or chloroform to a subject after he has suffered for some time, you hasten fatal apnœa, unless you administer CO_2 also. In India, according to Lauder Brunton, it is customary to partly smother a man who has been severely injured. It would probably be wise when a man's legs have been crushed in a railroad accident to hold a paper bag over his nose and mouth so that the excessive respiration of pain might not induce acute acapnia. In experiments in the laboratory we have found that when forced respiration is performed into a paper bag the excessive ventilation of the lungs is prevented and the subject at the end of the hyperpnœa, instead of passing into apnœa, continues to breathe normally. The same result may be accomplished by breathing through a tube. We have employed a piece of single tube bicycle tire, three to five feet in length. For the most part, however, the prevention of shock, even if the acapnia hypothesis prove true, will still consist in the prevention of pain.

On the topic of the therapy of shock, which the acapnia hypothesis suggests, I have carried out as yet only a few experiments. When a moderate degree of shock has been induced by irritation of afferent nerves or by exposure of the viscera, I find that it is possible to induce a rapid recovery of arterial pressure by the infusion into a vein of normal saline or of Ringer's solution saturated with CO_2. Then the animal is made to breathe an atmosphere of oxygen and CO_2 or else merely of oxygen supplied at the end of a long tube. Under these conditions it rebreathes the oxygen several times and thus the CO_2 which the subject itself produces is utilized to stimulate respiration and increase the otherwise insufficient oxygen intake. If the degree of shock previously induced is not too severe, not only do these measures of relief induce a rapid restoration of arterial pressure and respiration, but this restoration is maintained. On the other hand, in profound shock these measures fail to effect an ultimate recovery. Indeed, after the diminished blood stream has resulted in tissue asphyxia and acidosis no measure of relief, except perhaps hypertonic saline solution or transfusion of blood, can be of much use.

There are two methods of treating acapnial failure of respiration under anæsthesia. We find that if a soft catheter is inserted in the trachea down to the bifurcation of the bronchi and a gentle stream of oxygen gas is supplied, according to the

method devised by Volhard, the subject will lie for a very long time indeed in complete apnœa. By this method a supply of oxygen ample for all the needs of the tissues may be maintained. The oxygen should, however, be measured, and for a man should be not less than 400 cc. per minute. Under these conditions in animals reaccumulation of CO_2 proceeds relatively rapidly. In one case I have seen a dog in acute acapnia lie for 12 minutes without the slightest respiratory effort and at the end of this period recommence normal breathing. The oxygen jet had supplied ample oxygen for the combustion of the acidosis substances which would otherwise have been produced. This method of Volhard, therefore, accomplishes a double object. It prevents the acidosis of asphyxia at the same time that it allows the subject to recover from acapnia. I do not know whether surgeons would be willing to utilize it in the operating room. It requires some courage to leave a patient perfectly quiet and breathless—much more courage if it is a man than if it is a dog.

Another method of restoration of breathing has been tried upon dogs during apnœa with strikingly successful results. It consists in administering air or oxygen containing 5 or 6 per cent of CO_2 and in starting the subject to breathing by one or two artificial respirations. As soon as the normal tension of CO_2 in the lungs is thus restored spontaneous breathing immediately recommences and is maintained as long as the inspired air contains a sufficient quantity of CO_2 to stimulate the respiratory center. It will, I think, be advisable to use for this purpose oxygen and CO_2, and not merely air plus CO_2, for the purpose of preventing the acidosis of which I have spoken. Indeed, oxygen and CO_2 would combine the advantages of both methods for preventing fatal apnœa. It must be remembered that CO_2 is a powerful drug and one to be administered in small quantities only—never in greater concentration than 5 or 6 per cent. I have devised a simple gas meter which I believe may be useful for measuring the small quantities of CO_2 to be added to air or oxygen as a respiratory stimulant. It would be better to have the gases already mixed. I hope to be able to induce the manufacturers to supply tanks of oxygen containing 5 or 6 per cent of CO_2, and I hope to be able to persuade clinicians to use it.

This brings to a close what I fear is both a superficial and obscure presentation of the acapnia theory of fatal apnœa vera and of shock. I do not myself regard this theory as yet as anything more than a working hypothesis. I accepted gladly the invitation from your secretary to present it to you this evening because I felt that in this audience I should find men fitted to point out the shortcomings in the theory. I understand that it is your custom to discuss the papers which are presented before you. I assure you that I will appreciate it very highly as a great help to me in the final working out of this theory if you will now criticise it as severely as you possibly can—the more severely the better.[4]

[4] For the experimental data and references to the literature on which this paper is based see the American Journal of Physiology, 1908, XXI, p. 126; 1909, XXIII, p. 345; 1909, XXIV, p. 66; 1910, XXV, p. 310, and p. 385; 1910, XXVI, p. 260. On the clinical side of the subject see the paper of Malcolm, J. D.: Transactions of the Medical Society of London, 1909, XXXII, p. 289; and Gatch, W. D.: Journal of the American Medical Association, 1909, LIV, p. 775.

ON THE THREEFOLD PHYSIOLOGICAL ORIGIN OF URIC ACID.*

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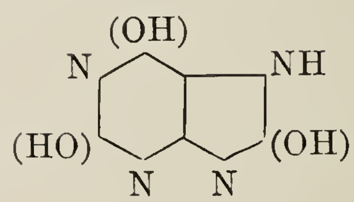
The uric acid of the urine is produced by three physiological processes which so far as we can see are not directly dependent upon one another. It is therefore necessary that in any discussion of the abnormal production of this substance, due consideration be given to all three sets of conditions under which it normally makes its appearance in the body. One of these processes is known as the nuclein metabolism and is concerned with the nucleic acids which constitute a large part of the material present in the nuclei of all cells. For a clear understanding of the nuclein metabolism it is advisable to discuss some matters of chemical structure.

The constitution of uric acid was established by a synthesis of Behrend (1), who proved that the substance is correctly represented as the trioxy derivative of a double ring consisting of a pyramidin ring and an imidazol ring united in the manner indicated in the formula



Starting with the uric acid of known constitution Fischer (2) prepared a substance having three chlorine atoms in place of the three hydroxyl groups and from this chlorine substitution product a large number of derivatives were prepared, including the mother substance of them all. This mother substance is called purine and the numerous compounds which Fischer prepared from its trichlor substitution product are known as purine derivatives. Four of them, viz., guanine, adenine, xanthine and hypoxanthine, are of great importance in dealing with the physiological origin of uric acid. Their relation to one another and to uric acid is shown in the follow-

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ing diagram in which purine with its three replaceable hydrogen atoms would be represented by $P\begin{cases}\diagup H(2)\\ -H(6)\\ \diagdown H(8)\end{cases}$

	Guanine (2-amido-6-oxypurine)	Adenine (6-amidopurine)
	$P\begin{cases}\diagup NH_2(2)\\ -OH(6)\\ \diagdown H\ (8)\end{cases}$	$P\begin{cases}\diagup H\ (2)\\ -NH_2(6)\\ \diagdown H\ (8)\end{cases}$
	$\downarrow$	$\downarrow$
Uric Acid (2-6-8-trioxypurine)	Xanthine (2-6-dioxypurine)	Hypoxanthine (6-oxypurine)
$P\begin{cases}\diagup OH\\ -OH\\ \diagdown OH\end{cases}$	$P\begin{cases}\diagup OH(2)\\ -OH(6)\\ \diagdown H\ (8)\end{cases}$	$P\begin{cases}\diagup H\ (2)\\ -OH(6)\\ \diagdown H\ (8)\end{cases}$
$\leftarrow$	$\leftarrow$	

It will be seen that adenine contains an amido group where hypoxanthine contains a hydroxyl group: otherwise the structure of the two substances is the same. It should, therefore, be possible to convert adenine into hypoxanthine. As a matter of fact the transformation can easily be accomplished: indeed the discoverer of adenine (Kossel) thus proved its relation to hypoxanthine (3). Not only can adenine be converted into hypoxanthine, but the experimenter must be constantly on his guard lest the transformation occur in some analytical procedure without his intention or even without his knowledge and thus lead to false conclusions.

The chemical relation of guanine to xanthine is the same as that of adenine to hypoxanthine; guanine and adenine are amido purines, xanthine and hypoxanthine the corresponding oxypurines. In both cases the amido compound can be converted into the oxycompound, water being taken up and ammonia liberated according to the general equation

$$R.NH_2 + H_2O = ROH + NH_3.$$

This reaction, in the most general sense of the term, is hydrolysis, but as it is not brought about by boiling acids it is more commonly known as disamidization.

Uric acid is a simple hydroxyl derivative of xanthine and xanthine likewise of hypoxanthine. By oxidation under proper conditions it is possible to convert hypoxanthine into xanthine and this in turn into uric acid. But it is necessary to observe that while the empyrical chemical relation of guanine to adenine is the same as that of xanthine to hypoxanthine, there is a structural difference between the two former which makes it impossible that one of these substances be directly converted into the other. While hypoxanthine can be directly oxidized to xanthine, adenine cannot similarly yield guanine, but would yield 6-amido-2 oxypurine. This by further oxidation might be expected to produce 6-amido-2-8-dioxypurine which by disamidization could pass into uric acid. Thus uric acid may theoretically be formed:

1. From adenine through hypoxanthine.
2. From adenine through 6-amido-2-8-dioxypurine.
3. From guanine through xanthine.

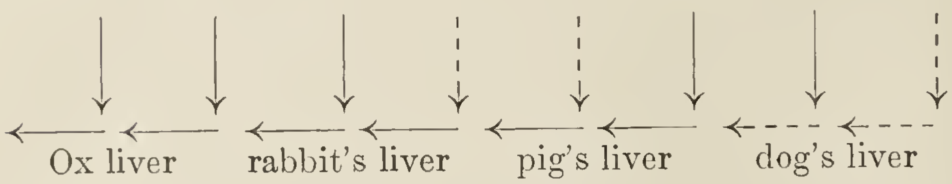
Other obvious theoretical possibilities do not concern us.

The physiological importance of these relations becomes apparent when it is stated that all nucleic acids, whether of plant or animal origin, yield equivalent quantities of guanine and adenine upon hydrolysis with boiling mineral acid (4). While this statement is rigidly correct, it is not in accordance with the results of the older experimenters, who found four purine derivatives among the hydrolytic products of nucleic acid. This apparent discrepancy has been brought about by a number of factors. In the first place, the method of hydrolysis employed in the older work was of such a nature that one can see how the two amidopurines first formed would of necessity be partly transformed into the oxypurines; but so far as concerns guanine it has been shown that when hydrolysis of nucleic acid is effected by ferment action at the body temperature and in a practically neutral fluid, there is no formation of the oxypurine (5). Again, there is a wide occurrence in the body of a substance called guanylic acid which yields guanine but not adenine. This substance is not to be regarded as a nucleic acid and its presence in various nucleic acid preparations has undoubtedly led to confusion in the relative quantities of guanine and adenine which nucleic acids produce (6). Lastly, there is considerable reason for supposing that the nucleic acid material employed by the older workers actually contained oxypurines as impurities. At any rate the concordant results of all modern investigations prove beyond question that nucleic acids, when properly prepared and hydrolyzed, yield equivalent amounts of guanine and adenine but no other purine derivative.

It has been repeatedly shown that when nucleic acid is submitted to the action of aqueous glandular extracts at the body temperature, the substance undergoes hydrolysis with the production of the purine derivatives guanine and adenine. As the hydrolytic agent in these extracts is destroyed by heat, varies in the extent of its action directly with time and possesses the attributes of a number of other active physiological agents, it is looked upon as ferment and has received the name "nuclease" (7). It has also been demonstrated that the two amidopurines (guanine and adenine) are converted into the two corresponding oxypurines (xanthine and hypoxanthine) by the action of thermolabile active agents present in the aqueous extracts of various glands (8). As the extracts of certain glands promptly disamidize relatively large quantities of one of the amidopurines but exert little or no action on the other, the conclusion has properly been drawn that two independent active agents are concerned in the disamidization, viz., "guanase" and "adenase" (9). Again, certain glands contain an active agent under whose influence hypoxanthine and xanthine are oxidized to uric acid. This oxidizing ferment, known as xanthoöxidase (10), is of course capable of exerting its action only in the presence of a proper supply of oxygen (air). Finally, when uric acid is digested at the body temperature with certain glandular extracts, the substance disappears, being probably converted into allantoin (11), which can be easily excreted.

Thus by the successive action of five independent physiological agents nucleic acid may be made to produce uric acid

and the latter be destroyed. These active agents have for sufficient reasons been called ferments, and are known specifically as nuclease, guanase, adenase, xanthoöxidase and uricase. With very rare exceptions all five of these nuclein ferments are not present in any one gland. Pig's liver exhibits xanthoöxidase to a marked degree, adenase much less so and guanase not at all, while pig's spleen promptly changes adenine into hypoxanthine, but exerts no action whatever upon guanine or hypoxanthine. Pig's spleen can disamidize adenine but not guanine (12). On the contrary, rabbit's liver can disamidize guanine but not adenine. This "distribution" of ferments is not only different for different glands, but varies to an unmistakable degree with animal species (13), a matter set forth in the following self-explanatory diagram, where solid lines are intended to indicate the presence of a ferment, dotted lines its probable absence or slight activity. The question considered is the distribution of the nuclein ferments in the livers of four animal species.



Thus the ox liver can convert into uric acid all purine material formed from nucleic acid, the rabbit's liver only one-half, the pig's liver the other half, while the dog's liver seems incapable of forming uric acid from any purine precursor (12). Such a variation with species clearly suggests that the distribution varies in each species with age. This has been proven in a number of cases. Thus the ferments of pig's liver do not simultaneously appear, but at a certain stage of embryonic development adenase can be shown before xanthoöxidase has made its appearance (14). So also one of the most active ferments of the adult human body (guanase of the liver) is not present in the embryo (15).

This great variation of purine ferments with animal species makes it necessary to find the distribution in the case of man. The difficulty of such an investigation is apparent; one cannot easily get possession of normal human organs. It occurred to us that some idea of this question might be gotten by examining a large number of pathological cases and noting the constant factors. While this work was in progress a publication appeared by Schittenhelm and Schmid (16), stating that all human organs contain all five of the nuclein ferments. The presence of uricase in the liver was specially noted. Uric acid was introduced into aqueous extracts of the organ and air passed into the material as it digested at the body temperature. After the digestion uric acid could not be found and as the method employed was such that the substance if present could not escape detection Schittenhelm and Schmid did not hesitate to announce that human organs are well supplied with uricase, which normally brings about the destruction of part of the uric acid formed from the nuclei.

From chemical experiments with gouty patients, Schittenhelm and Brugsch (17) subsequently formulated their widely known theory of gout. Divested of its unessentials, this theory is to the effect that in gout there is a disturbance of the normal activity of the ferments of the nuclein metabolism and especially of uricase the ferment that causes the destruction of uric acid; so that while normally a portion of the uric acid formed in the body is converted into products that are soluble and easily excreted, in gout the absence of uricase must lead to a condition in which uric acid becomes excessive and is laid down in the tissues. Shortly after the announcement of the Brugsch-Schittenhelm theory, the organs of a gouty patient who died in this hospital were placed at our disposal. Attention was naturally directed to the question of uricase in the liver. Aqueous extracts of this organ were digested with uric acid under conditions well adapted to the activity of uricase, but in spite of all efforts to bring about its destruction, the uric acid could be recovered unchanged. We were, therefore, of the opinion that we had actually proven a condition in the gouty liver which Schittenhelm and Brugsch had predicted from the results of their clinical work (15). At this time there appeared an article by Wiekowski (18), who was unable to demonstrate uricase in *normal* human organs. We were easily able to confirm Wiekowski's results. An aqueous infusion of liver from a case of aneurism was treated with uric acid and under conditions most favorable to its destruction, but in all experiments a reasonable amount of uric acid could be recovered unchanged. An experiment was also made in which no uric acid was added to the liver extract, but in spite of all efforts to demonstrate uricase a small amount of uric acid was found among the products of self-digestion: so that not only is the human liver incapable of destroying uric acid when added from without, but cannot even destroy the small amount of uric acid formed in a self-digestion from the nucleic acid of the gland (15).

There is, moreover, no demonstrable difference between gout and aneurism, so far as concerns the nuclein ferments, other than uricase (19). As already stated, Schittenhelm and Schmid found all of the nuclein ferments present in aqueous extracts of all human organs, and this observation undoubtedly formed the basis of the theory of gout which Schittenhelm and Brugsch subsequently proposed. The results obtained by Miller and by Winternitz with human organs do not substantiate the findings of Schittenhelm and Schmid. Miller and Winternitz find that, like every animal species thus far examined, the human species has its characteristic ferment distribution.

1. Guanase is easily proved present in all human organs. Relatively large quantities of guanine are rapidly and completely changed into xanthine by aqueous extracts of muscle, spleen, liver, kidney, lung and pancreas.

2. Adenase cannot be proved present in any human organ. Relatively small quantities of adenine can be almost quantitatively recovered after digestion for months with human organ extracts, but a small amount of hypoxanthine can also be found among the products. Whether this trace of hypoxanthine represents a slight activity of adenase, which disappears as digestion proceeds or is entirely apart from the nuclein metabolism, is a question at present in dispute. We have taken the ground that as muscle always contains hypo-

xanthine, which does not come by the action of adenase on adenine, this trace of hypoxanthine constantly found in digested glands may be better accounted for as coming from the small amount of muscle in the glands than as representing the slight activity of an expiring ferment.

3. Xanthoöxidase is in great activity in human liver, but is confined to this organ.

4. Human organs, by their inability to destroy uric acid, differ from the organs of the lower animals.

With matters of disputed interpretation we are not here concerned. In whatever way one is disposed to view the facts they are the same in gout as in aneurism, so that whatever is the cause of gout, it is not a derangement of any of the ferments of the nuclein metabolism, so far as this can be demonstrated with organ extracts.

Shortly after the publications of Wiekowski, of Winternitz and of Miller, Schittenhelm made the following interesting report of his recent examination of human organs (20, 21).

1. Guanase is undoubtedly present in all human organs.

2. Added adenine can for the most part be recovered unchanged after digestion with human organ extracts.

3. Xanthoöxidase is confined to the liver.

4. Uric acid can, to a large extent, be recovered unchanged after digestion with extracts of human organs, but there is some loss. Concerning this disappearance of a small fraction of the added uric acid Schittenhelm remarks that it is too small to be looked upon as evidence of the destroying ferment and too large to represent an analytical loss. It seems a pity that Schittenhelm did not state this last proposition in the form of a syllogism.

The presence in tissue extracts of a small amount of hypoxanthine, which cannot be accounted for as a product of nuclein metabolism, brings us to a discussion of the second method by which uric acid is formed in the animal body.

In the course of his well-known work on the origin of endogenous uric acid, Burian (22) observed that when hypoxanthine is withdrawn from a surviving dog's muscle by perfusion, an equal quantity of the base is produced in the muscle to take its place, so that the amount of this constituent in the tissue thus tends to a constant value. The conditions of his experiments were of course such as to preclude migration of hypoxanthine from any other part of the body. Hence he concludes that the base is being continually formed in the living muscle from some unknown precursor which is not a constituent of the leucocytes. As the amount of hypoxanthine given up to the perfusion fluid was found very much greater after stimulation than after a period of rest, Burian establishes a clear causal connection between muscle stimulation and the production of muscular hypoxanthine.

Hypoxanthine is thus being continually formed in dog's muscle, but as Leonard (23) has shown, dog's muscle extract contains no adenase; nor does the surviving dog's muscle exhibit this ferment (24). Taking into consideration all that we know of the physiology of muscle, it seems fair to conclude that the chemical changes involved in muscle contraction are probably of the same general nature in all muscles. Whether this be rigidly true or not it has been shown that, as is the case with voluntary muscle, the predominating base of involuntary muscle is hypoxanthine, unaccompanied by xanthine, its constant and necessary companion in the nuclein metabolism (25). There seems ample justification for assuming that hypoxanthine is just as characteristic and necessary a muscular constituent as is creatinine or sarcolactic acid. But it is just as true that adenase is not a muscle ferment. Of the muscle extracts of the dog, pig, rabbit, man (26) and ox we have been able to prove its presence only in the case of the last-named species; but the hypoxanthine of ox muscle is not appreciably greater than that of dog's muscle, which latter, by the consent of every one, is practically free from any function that can bring about the formation of hypoxanthine from adenine. Hypoxanthine is not only found with regularity in muscle tissue which does not contain adenase, but in the muscles of certain animal species in which adenase can neither be demonstrated in extracts of any of the organs nor of the combined organs of the entire animal. This is notably true of the rat (27) and is in harmony with Nicolaier's (28) discovery that in these animals subcutaneously injected adenine is oxidized, but reaches the kidneys without disamidization, where it gives rise to deposits of 6-amido-2-8-dioxypurine.

It is obvious that hypoxanthine formed in muscle will be converted into uric acid when it circulates through an organ containing xanthoöxidase, and this is the second method by which uric acid is formed in the body.

A number of considerations lead to the probability that uric acid may be produced in a manner that is different from the two which have been considered. The earlier studies of the nuclein ferments had shown that while one organ does not as a rule contain all of these active agents, yet every species was found supplied, in one organ or another, with the ferments necessary for the formation of uric acid from guanine, from adenine, or from both. But this is not true of the rat (27). The organs of this animal exhibit guanase uniformly and strongly, but the xanthine thus formed is not oxidized to uric acid by any or all of the organ extracts. Yet the rat's urine contains uric acid. The suggestion is clear that this organism has at its disposal some other method of producing uric acid, and this method is indicated in no uncertain way by the brilliant work of a group of Italian chemists under the direction of Ascoli (29).

It has been long known that uric acid is destroyed when an aerated solution of the substance is perfused through the surviving dog's liver. Ascoli now shows that if the perfusion fluid containing the destruction products be saturated with carbon-dioxide and again perfused, uric acid makes its appearance. It will be seen that we are here dealing with two ferment actions, one of which is exerted in the presence of oxygen and destroys uric acid; the other acts in the presence of carbon-dioxide and produces uric acid. But this destructive and producing action are not reversed actions of the same ferment, for, if a bloodless liver be perfused with an oxygenated solution of uric acid the acid is destroyed, while there is no production of the substance upon subsequently perfusing the blood-

less organ after saturation with carbon-dioxide. Again, the destruction products of uric acid by uricase are probably allantoin and urea. The producing ferment forms uric acid from dialuric acid and urea, but not from allantoin and urea. All of the results described can be obtained just as well with organ extracts as with the surviving organs. Uric acid is not produced by carbonated blood nor by an aqueous extract of the bloodless liver, but is produced by a mixture of the two. If the bloodless liver extract be boiled before mixing with the blood, the results are in no way altered; but if the blood be boiled the production of uric acid no longer occurs. Plainly the producing ferment is present in the blood and the organ furnishes the activator, while uricase (also guanase (30)) is found in the bloodless organ extract. Thus uric acid can be formed in the animal body by a process that involves neither a purine ring nor a purine ferment, and this mode of formation has of course received no consideration in any theory of gout.

It is not altogether agreeable to learn that a difficult problem in experimental medicine, once regarded as solved, is again opened to discussion. A degree of satisfaction is to be gotten upon reflecting that an exposed error in science is a double advance, "but we are not here concerned with hopes or fears, only with the truth so far as our reason permits us to discover it: and I have given the evidence to the best of my ability."

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INTRATHORACIC DISPLACEMENTS IN PULMONARY TUBERCULOSIS.*

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The following supplementary report† deals with the changes brought about in intrathoracic relations as shown by skiagrams of cases of pulmonary tuberculosis, studied clinically before and after the taking of the X-ray plate. I will confine myself simply to the more salient features of this study, which deals with the alterations in the position of aorta, heart, and diaphragm. The presence or absence, of enlarged bronchial glands, and of calcareous infiltration of the costal cartilages of the ribs is also briefly considered.

When such a study is carried out with technical precision, it would seem to leave little room for error. Because with the use of the modern tubes and coils, and instantaneous exposures, the resulting skiagrams are so clear cut and definitive as to give an admirable geographical chart. I believe that such a study gives more satisfactory results in regard to the position of the organs in life than those obtained by autopsy, for in the latter there is the post mortem change, due to alteration in intrathoracic pressure or to other strictly post mortem influences, and there is also the trauma of the autopsy and consequent derangement of relations, and finally there is the question of elapsed time. I feel further that purely clinical studies of this nature, when unconfirmed or unchecked by röntgenology, are without much accuracy or value, except in so far as in certain instances the personal equation of the investigator has given them such.

I shall not discuss the use of the X-ray from the standpoint of early diagnosis, nor even in its relation to the later pathological changes. The value of röntgenology in the study of pulmonary tuberculosis, as supplementary to physical examination, is so generally recognized as to need no exposition. Röntgenology must not, of course, be considered as having

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† See preliminary report, entitled: The Effect of Tuberculosis on Intrathoracic Relations, Am. J. Med. Sc., May, 1910. This article contains the case histories in full to which reference is made in the present paper. The author desires to express his thanks here to Dr. A. O. J. Kelly, for permission to publish this supplementary report in the Johns Hopkins Hospital Bulletin.

solved the problems of physical diagnosis of the chest, but it helps to elucidate them and to confirm the clinical findings. It has not and never can supplant nor minimize the importance of the time-honored clinical methods, but on the contrary it should serve a useful purpose in stimulating more exact methods, because the possibilities of physical diagnosis are extended from the information and suggestions gleaned from the X-ray. As Minor has well said in an address before this Society, "it is the corroboration which the X-ray brings to the results of our regular examination that is one of its most valuable features."

The cases from which this study is made, were skiagraphed by Dr. Charles Lester Leonard, of Philadelphia, and were in some instances patients from the Pennsylvania State Dispensary for Tuberculosis (Phila.), and in others, from private practice. The majority of the cases were moderately advanced and advanced cases (Class II and III of the National Tuberculosis Association classification), though the only selection used was in the financial ability of the patient to bear the expense of the skiagrams. The number here reported is too small (that is 81 cases) to warrant me in drawing any very definite conclusions, but the results are at least suggestive, and the conclusions which I do present relate only to this series.

I shall not attempt at this time to discuss the data gleaned from this study in the light of present knowledge or views, but shall content myself with merely recording the details noted, pointing out where in certain instances the conclusions drawn are at variance with the views or opinions of others.

The Aorta and Heart.—It should be noted that quite frequently the aorta is displaced in advanced pulmonary tuberculosis as well as the heart and in the same direction. In marked displacements of the heart this is the rule and such displacement was noted clinically and confirmed by the X-ray in 14 cases. Rarely the aorta may be drawn out of position, while the heart is unaffected. The error is sometimes made of interpreting the physical signs of a displaced aorta as being those of enlarged glands or of aneurismal dilatation. With an area of dulness to the right or left of the sternum in the second or third interspace, with or without expansile pulsation, accompanied by much displacement of the heart, the conclusion that the aorta is displaced is warranted, in the absence of definite signs of aneurism. Rarely an aneurismal dilatation of the aorta may be present.

In 67 per cent of the cases the heart was not displaced (that is in 55 cases). Thus it is noteworthy that in the present series very many of which were advanced or far advanced cases the heart in the majority of instances was not displaced. There seems no doubt about this conclusion, and I therefore feel that those who hold that displacement of the heart is a reasonably constant sign or accompaniment of pulmonary tuberculosis are in error. Turban (1) makes the statement that "it is exceptional to find the heart in its normal position in advanced chronic tuberculosis" while Pottenger (2) says that displacement of the heart is a "typical and cardinal symptom" of tuberculosis of the right apex.

Absence of displacement is much more common, in fact almost the rule, in acute infiltrations and consolidations before fibrosis and contraction have taken place. In many instances even where the lesions were widespread and often destructive, the heart was not displaced. This was true in 25 advanced cases. For instance in a case,[a] with cavitation at the right apex and infiltration of the entire upper lobe, the heart was not displaced due to pericardial adhesions over the apex which could be plainly seen. In a second case,[b] with large cavities in both apices and much fibrosis, the heart was not displaced, possibly on account of the symmetrical character of the lesions, or possibly from adhesions. In a third case,[c] with left sided localized pneumothorax, the heart was not displaced. In a fourth case,[d] with a large cavity on the right side and complete consolidation of the right upper lobe and moderate infiltration on the left side, the heart was not displaced.

There would seem to be three factors which may play a part in preventing cardiac displacement in advanced pulmonary tuberculosis. The first and most important is, of course, the existence of adhesions which bind down the heart; the second, where the destructive lesions are relatively symmetrical in extent, the tendency to displacement to one side or the other seems in certain instances to have been modified and overcome by the equality of the traction exerted on both sides; the third, a left sided localized pneumothorax (which exists more frequently than is generally supposed and is practically always overlooked) may hold the heart in place even in the presence of extensive destructive lesions at the left apex. Thus in one case[e] with a large cavity at the left apex, the heart was much displaced to the left until the development of a small pneumothorax, which forced it promptly back into a normal position. The physical signs of this localized pneumothorax were most inconclusive, but the condition was plainly discernible in the skiagram.

The heart was displaced in 33 per cent of this series, in 15 cases to the right, in 4 cases to the left, in 3 cases upward and to the left and 5 cases in the antero-posterior position to be described later. Thus it was displaced twice as often to the right as to the left. I cannot, therefore, agree with the statement of Lawrason Brown (3) that "marked displacement of the heart occurs much more frequently to the left than the right."

When the pulmonary lesions are of fairly symmetrical character on both sides, the heart if displaced is more commonly drawn to the right than to the left. In these cases there is usually evidence to show that the primary and older lesion is on the right. When the lesion is more extensive on the left the heart is not so regularly displaced nor to the same extent, as in corresponding right-sided lesions. Rarely the fibrosis of

[a] Case XIII.
[b] Case XXIII.
[c] Case XXIV.
[d] Case XXXIII.
[e] Case LXI.

lung and pleura may be so great or of sufficient density to obliterate the boundaries of the heart.[f]

In 5 cases the heart occupied, what for want of a better term I have called the antero-posterior position. In this position the heart assumes a long narrow appearance, as if it were turned upon its vertical axis. It should be noted that in all these cases, there were far advanced destructive lesions on both sides, and it might appear that the combined effect of the traction exerted under these conditions, had resulted in drawing the heart upward and inward, thus causing the apex to swing around. Attention has not, so far as I am aware been called to this very definite position of the heart in certain advanced cases, previous to my description of it in August, 1909.

In long, narrow chests the heart assumes a more oblique position. The angle formed with the liver on the right is less acute and the left boundary is appreciably more vertical. The heart also assumes an appreciably more oblique position during deep inspiration.

In many cases the skiagrams show an interesting feature which is not demonstrable clinically, namely, that during systole of the heart there is an area between the lower boundary of the heart and the diaphragm (a cardio-phrenic space) of about the extent of one centimeter, which distinctly transmits the rays. The limits or extent of the cardiac excursion may also be seen in many cases. In 4 cases, distinct pericardial adhesions could be seen. The heart appeared normal in size both in the X-ray plates and to physical examination, in all the cases with 4 exceptions. In 3 of these the enlargement was practically confined to the right side, and the lungs were markedly emphysematous. In one case[g] there was a general hypertrophy. There was no evidence of an organic lesion in the series, though in some cases soft systolic murmurs were audible in the mitral and pulmonary areas.

The Diaphragm.—The skiagrams were taken under full inspiration. In 41 cases (50 per cent) the diaphragm was unaffected by the pulmonary lesion. In 19 cases it was elevated on the right side, in 7 cases on the left; in 7 cases it appeared to be elevated on both sides; and in 7 cases it was not visible or determinable on account of the density of the adjacent involvement of lungs and pleura.

In every case in which the heart was displaced the diaphragm was elevated on the side toward the displacement, and in the cases where the heart assumed the antero-posterior position the diaphragm appeared elevated on both sides. There was one exception to this rule which does not properly apply as such, but in a case,[h] which had been operated on for left sided empyema, some years previously, there was collapse of the chest wall, with consequent dragging upward of the diaphragm on the left side, while the heart was displaced to the right.

The diaphragm was affected in 18 cases in which the position of the heart was normal. In other words, the diaphragm was more sensitive to, or affected by, the presence of a pulmonary lesion than the heart in 19 per cent of the cases. This was true in 11 advanced cases, as well as in 6 of the earlier cases, and yet in 10 advanced cases where one would have expected to find the diaphragm affected, it was not apparent (except in limitation of pulmonary excursion), either to physical examination or in the plates. Thus in cases[i] of relatively slight involvement the diaphragm may be elevated on the affected side; while in cases[k] with marked involvement and even cavitation the diaphragm may not be elevated but in these cases the heart is not displaced. Thus the diaphragm had responded, in change of position, to the pulmonary lesion in half the cases.

The Peribronchial Lymph Nodes.—In every case in this series the cervical glands were enlarged to palpation. It would seem probable that the peribronchial glands are also affected in all cases, though this could not be deduced from the skiagrams. In 59 per cent of the cases enlarged glands could be seen in the plates. With the exception of about 20 cases all the cases in which enlarged glands were visible were either relatively early or moderately advanced, without marked breaking down of tissue; while in the majority of the far advanced cases the glands did not show. It would appear as if there might be two explanations for the absence of glands in the majority of plates in which they were not visible, namely, that their presence was concealed by the area of involvement, or what appears more likely, that with the advance of the disease the glands had softened or broken down and so failed to give rise to a shadow. There were usually only three or four glands or clusters of glands noted in any one plate, and in a number of instances they appeared to be calcified.

Calcification of the Costal Cartilages.—The presence of calcareous infiltration in the costal cartilages was noted in only 12 cases. It would appear to be grossly absent in many cases in which its presence might be expected and where it could no doubt be demonstrated microscopically, and it was generally noted in the advanced chronic type of the disease, though there were exceptions to this. It was usually confined to the costal cartilage of the first rib, though in several instances it involved them all. In many of the advanced cases the involvement was of sufficient density and extent to have concealed the presence of calcification in the cartilages of the first rib, but there was no calcification in the costal cartilages which could be properly studied.*

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[f] Case IX.

[g] Case XIX.

[h] Case XXVII.

[i] Case XXII, as type.

[k] Case XIII, as type.

* The summary of each case with classification and details of lesions will appear in a final report.

BLOOD CULTURES IN PNEUMONIA.

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The more recent blood-culture studies in acute lobar pneumonia have led to the general conclusion that in most cases, at least, the disease must be regarded as a general pneumococcæmia. But the results have been so discordant that the question cannot be considered definitely settled. Some investigators have reported growths in 90 per cent or more of their cases; while others obtain them much less frequently. Numerous reasons have been advanced to explain the varying results. We have attempted to investigate some of the points in controversy in a small series of cases from the medical clinic of the Johns Hopkins Hospital, which we are allowed to report through the kindness of Professor L. F. Barker.

The blood was obtained from the median-basilic vein in a sterile syringe of 15 cc. capacity, and was placed in culture media directly at the bedside. The media employed in each case and the degree of dilution are indicated on the chart. The medium called "special" was a 10 per cent peptone, 2 per cent glucose water, made up according to the directions of Wiens (1), who reports better results with this than with any other media. Cultures made in 1 to 10 dilution were in test tubes; the higher dilutions were in flasks.

Of 25 cases studied, cultures of the pneumococcus were obtained from the blood of 14; i. e., in 56 per cent. In the series, 5 cases were fatal (20 per cent), and in all these the cultures were positive. Of the 14 positive cases, 36 per cent died. In 7 of the positive cases, a second culture was taken after the crisis or during lysis, but no growth was obtained. An analysis of the 11 negative cases shows that in 4 (16, 18, 20, 22) the cultures were taken on the day of the crisis; in 3 (17, 24, 25) on the day preceding the crisis. Cases 15 and 18 were unusually mild. Cases 19 and 23, however, were more severely ill than many of the positive ones.

As soon as growth was discovered in the cultures, transfers were made to blood agar slants. In every case but one, growth was evident within 18 hours. Every culture was examined carefully at the end of 24 and 48 hours, both microscopically and by making transfers to blood-agar slants before being reported negative. Capsules were easily demonstrated in every case. Further studies of the cultural characteristics identified the organisms as pneumococci. In one case the thick, watery growth on agar, the arrangement in chains, and the easily staining capsules indicated the variety commonly known as *Streptococcus mucosus capsulatus*. Tests of the phagocytability of the organisms by normal human serum and leucocytes were made immediately after isolation. In every case the organism was not phagocytable.

The media used in each case, and the dilution, are given in detail on the chart. In but two cases were agar plates employed. In Case 3, one to three colonies appeared on each plate. In Case 4 no growth was obtained in any medium at the first culture. In all cases some of the following media were used: litmus milk tubes and flasks, broth tubes and flasks, glucose-broth flasks and Wiens' special 10 per cent peptone, 2 per cent glucose water in tubes and flasks. The dilution of the blood was determined in each case. Most of the cultures were at a dilution of 1 to 10, and 1 to 30; but growth was obtained at a dilution of 1 to 5, and of 1 to 75. In the series of positive cases, the milk tubes showed no growth in two, and Wiens' special medium also was negative in two. Plain broth gave growth in 7 of 9 cases, and glucose broth in all of the 10 cases in which it was used. On the whole, it may be said that when obtained at all the pneumococcus grew about equally well in all the liquid media. The examination of the cultures has to be made promptly, for in many cases it was found that the culture died out after 48 hours.

From so small a series as this no final conclusions can be drawn. Two points, however, may be mentioned: (1) positive cultures were obtained in 56 per cent of the cases of an epidemic in which the mortality was only 20 per cent; and (2) the organism was easily obtained.

Prochaska (2, 3), in Zurich in 1901-1902, obtained positive cultures in 100 per cent of his cases. In his series of 40 cases, the mortality was 20 per cent. Many of them were mild. He used liquid media in varying dilutions, finding agar unsatisfactory. He obtained growth in 2 cases one day after crisis, and in 1 case two days after crisis.

Rosenow (4, 5), in Chicago, reported 91 per cent positive cultures in a series of 175 cases, with a death rate of 40 per cent. As a medium he used broth (chiefly) in a dilution of from 1 to 50 to 1 to 75. The percentage of failures to obtain a growth was higher during the 36 hours preceding the crisis than earlier in the disease, although he obtained growth in a few cases as late as 48 hours after the crisis. He also obtained growth 12 hours after the initial chill, before signs appeared in the lungs.

Kinsey (6), 1904, in Chicago, made a parallel series of cultures; in one using 8-9 cc. of blood in 50 cc. bouillon, with growth in 12 per cent; in the other, using a dilution of from 1-15 to 1-20, with growth in 76 per cent. His death rate was 32 per cent. He concludes that pneumococci are present in all cases, and that technical difficulties sometimes prevent their isolation. He finds as the most suitable method the use of liquid media in a dilution of 1-15 or 1-20.

In contrast to these results are those of Schottmüller (7),

Case No.	Sex.	Color.	Age.	Day of Disease. Admission.	Crisis.	Lysis.	Death.	Blood Culture. Day of disease.	Days before recovery or death.	Media.	Dilution.	Results.	Remarks.
1	M.	W.	43	8	....	....	10	9	— 1	Special	1—25	+	Extreme toxæmia. Autopsy.
										Gluc. broth	1—75	+	
										Milk	1—10	+	
										Special	1—10	+	
2	F.	B.	43	11	....	....	18	13	— 5	Gluc. broth	1—20	+	Acute ulcerative endocarditis. Meningitis. Abscess of lung. Autopsy.
										Milk (2)........	1— 5	+	
										Broth	1— 5	+	
3	M.	B.	50	1	....	......	7	4	— 3	3 agar plates...	1— 5	+	Streptococcus peritonitis, following appendicitis. Operation. Pneumonia 3 days after operation.
										Milk	1—10	+	
										Gluc. broth	1—30	+	
										Broth	1—10	0	
4	F.	W.	(?)	......	....	....	......	......	....	3 agar plates...	....	0	Meningitis. Patient entered hospital at the end of pneumonia with pulmonary signs still present. Date of onset not known.
										Bile	....	0	
										Milk	....	0	
										Special	....	0	
										Gluc. broth	....	0	
										Gluc. broth	1—30	+	
										Special	1—30	+	
										Special	1—10	+	
										Milk	1—10	+	
5	F.	B.	44	5	....	....	10	6	— 4	Broth	1—30	+	After 24 hours all negative. At 48 hours broth flask +. After 72 hours milk tube +.
										Special	1—30	0	
										Special (2)......	1— 5	0	
										Milk	1— 5	+	
6	M.	B.	24	4	10	....	......	5	— 5	Broth	1—40	+	Temperature about 100° F. at second blood culture.
										Special	1—25	+	
										Milk (2)........	1—10	+	
										Special	1—10	+	
								13	+ 3	Same media	....	All 0	
7	M.	B.	25	6	....	10–18	.....	8	— 2	Gluc. broth ...	1—30	+	Pneumonia migrans.
										Special	1—30	+	
										Milk	1—10	+	
										Special	1—10	+	
								16	......	Same media	....	All 0	
8	M.	B.	25	6	....	15	......	8	— 7	Milk	1—30	+	
										Gluc. broth	1—30	+	
										Milk	1—10	+	
										Broth	1—10	+	
										Special	1—10	+	
								20	+ 5	Same media	....	0	
9	F.	B.	20	3	....	....	......	4	....	Milk	1—30	+	Empyema 32d day. Signs on admission obscure. Diagnosis by blood culture. Gluc. broth + 18 hours. Milk + 3 days.
										Gluc. broth	1—30	+	
										Broth	1—10	0	
										Milk	1—10	0	
10	M.	B.	24	2	12	....	......	3	— 9	Milk	1—30	+	
										Gluc. broth	1—30	+	
										Special	1—10	+	
										Milk	1—10	+	
										Broth	1—10	+	
								14	+ 2	Same media	....	All 0	
11	M.	W.	40	4	....	8–10	......	4	— 4	Gluc. broth	1—30	+	Second blood culture on 3d day of normal temperature.
										Broth	1—10	+	
										Milk	1—10	+	
										Special	1—10	+	
								13	+ 5	Same media	....	All 0	
12	M.	W.	18	2	....	9	......	3	— 6	Special	1—30	0	Empyema 14th day.
										Special	1—10	+	
										Special	1—10	0	
										Milk	1—10	Cont. animat'd	
								12	+ 3	Same media	....	All 0	

Case No.	Sex.	Color.	Age.	Day of Disease. Admission.	Crisis.	Lysis.	Death.	Blood Culture. Day of disease.	Days before recovery or death.	Media.	Dilution.	Results.	Remarks.
13	M.	B.	20	3	....	8–38	......	5	— 3	Special .... Gluc. broth .... Special (2) ..... Milk	1—30 1—30 1—10 1—10	+ + + +	Delayed resolution. Temperature 99.5° F. at second blood culture.
								15	....	Same media	....	All 0	
14	M.	B.	21	4	12	....	......	5	— 7	Broth .... Milk .... Special	1—75 1—10 1—10	+ + +	Blood 5 cc.
								13	+ 1	Same media	....	All 0	
15	M.	B.	26	1	5	....	......	2	— 3	Gluc. broth .... Milk .... Broth	1—30 1—10 1—10	0 0 0	Unusually mild case.
16	F.	W.	32	7	....	7–9	......	8	0	Gluc. broth .... Milk .... Broth	1—50 1—10 1—10	0 0 0	Blood 5 cc. Taken during lysis.
17	M.	W.	17	7	9	.. ..	......	8	— 1	Milk .... Gluc. broth .... Milk .... Broth	1—30 1—30 1—10 1—10	0 0 0 0	Otitis media, 16th day.
18	M.	B.	24	3	9	....	......	4	— 5	Milk .... Gluc. broth . Broth .... Milk	1—30 1—30 1—10 1—10	0 0 0 0	Continued slow pulse. Respiration 24. Very mild case.
								9	0	Same media	....	All 0	
19	F.	W.	12	3	... .	....	......	4	....	Gluc. broth .... Milk .... Milk .... Broth	1—30 1—10 1—30 1—10	0 0 0 0	Pseudo crisis on 6th day. Interlobar empyema. Operation 22d day. Pneumococci in pleural fluid.
								16	....	Gluc. broth ... Milk .... Milk .... Broth	1—30 1—30 1—10 1—10	0 0 0 0	
20	M.	W.	34	9	....	10	.....	10	0	Gluc. broth ... Milk (2)........ Broth .... Special	1—30 1—10 1—10 1—25	0 0 0 0	Case from North German Lloyd Steamer.
21	M.	W.	18	3	....	(?)	......	4	—	Gluc. broth .... Milk (2)........ Broth (2)....... Special	1—30 1—10 1—20 1—25	0 0 0 0	Indefinite physical signs. Broncho pneumonia (?) Very gradual fall in temperature. Case from North German Lloyd Steamer.
22	M.	W.	25	5	5	....	......	5	0	Broth .... Broth .... Special .... Milk	1—30 1—10 1—10 1—10	0 0 0 0	Blood culture on day of crisis.
23	M.	W.	1	......	8–22	....	.....	2	— 6	Same as 2d culture.	....	0	Parotitis.
								4	— 4	Special .... Milk .... Broth .... Special .... Special	1—25 1— 5 1— 5 1— 5 1— 5	0 0 0 0 0	
24	M.	B.	18	4	7	....	......	6	— 1	Special .... Broth .... Milk .... Special .... Broth	1—50 1—50 1— 5 1— 5 1— 5	0 0 0 0 0	Culture taken day before crisis.
25	M.	B.	27	5	7	....	.....	6	— 1	Gluc. broth .... Special .... Special (2)...... Milk	1—50 1—40 1—10 1—10	0 0 0 0	Post critical rises up to 14th day. Temperature 100° F. at second blood culture.
								9	+ 2	Same media	....	All 0	

of Hamburg (1905), who obtained only 23 per cent positive cultures in a series of 209 cases. He used agar, making seven plates out of 10 to 20 cc. of blood. He obtained one positive result on the day of crisis. He got growth only in severe cases and considers a positive culture of bad prognostic value. He made comparative tests of liquid and solid media, and does not think technical difficulties explain the difference between his results and those of Prochaska: sarcastically remarking that "if Prochaska got such constantly positive results, then the explanation must be that pneumonia in Zurich behaves differently from pneumonia in Hamburg."

Similarly low results were obtained by Cole (8), in this clinic in 1900-1901. He reported only nine positive cultures (30 per cent) from a series of thirty cases with a mortality of 43 per cent. He used 10 to 15 cc. of blood; and as media, milk and broth in flasks, "in order to dilute the blood further, and so to overcome the bactericidal effect of the blood." He got positive cultures only in fatal cases, though not in all of these; and considered a positive culture as of bad prognostic value.

Wolf (9) (1906) emphasized especially the presence of the organism in the circulating blood after crisis. In 16 cases positive before crisis 6, or 37 per cent, were positive after crisis; 3 in uncomplicated cases 8 hours after crisis; and 3 in cases of delayed resolution, 7, 16 and 17 days after the fall in temperature; 1, one day, and 1, two days after normal temperature, and 1, three days before temperature became normal. The organisms obtained were not phagocytable by normal human, dog or guinea pig leucocytes in normal serum, or by the leucocytes and serum of the convalescent cases from which they were isolated, and were as virulent for rabbits as were the precritical organisms from the same patient. Wolf concludes that crisis cannot be associated with a sudden disappearance of organisms from the blood or with a change in their virulence.

Wiens (l. c.), in Breslau (1908), reports a series of 33 cases with 79 per cent positive results in which the death rate was 18 per cent. Several cases were positive during the fall of temperature at the beginning of crisis or lysis, and one case was positive one day after crisis. Two were positive the day before crisis. He concludes that bacteriæmia is constant in pneumonia if proper fluid media are used, and lays stress on his 10 per cent peptone, 2 per cent glucose water.

The following conclusions may be drawn from a summary of these reports:

(1) In certain epidemics blood cultures in pneumonia are positive in a majority of all cases.

(2) In such cases the results have no prognostic value.

(3) Pneumococci may be obtained at times from the blood of patients after crisis.

(4) The failure to obtain organisms in the blood is due in part to technical difficulties, in part to other factors.

These reports also furnish some basis for speculation as to the nature of the other factors causing the still varying results in the study of this question. The pneumococcus is an organism very susceptible to environment. A vigorous growth in one medium may not reproduce itself when transferred to media of other composition. This is especially true of cultures in milk, which may be very active and yet may not grow at all when transferred to blood agar, an equally good culture medium. The uncertain viability of the pneumococcus may also be inferred from the assertion of Rosenow (l. c.) that he was able to demonstrate the organism in smears from the blood of pneumonia patients from whom he could not isolate it by cultural methods. Aside from the slight differences in culture media, which in making cultures from the blood appear to be of little importance, it would seem the explanation must be either that the infective agent is not identical in all cases, or that the changes it undergoes in the human body vary greatly.

One point that possibly may have some significance, though hitherto neglected, is the matter of locality. Thus, acute articular rheumatism, a disease resembling pneumonia in many respects, varies considerably in its manifestations in different places. What is apparently the same disease is seen under quite different aspects in London and Baltimore. In other infectious diseases a similar difference in behavior may be noted in different places and at different times. It would seem possible that in pneumonia differences in the infectious agent itself, due to environment, or to locality, might play some part in explaining the difference in results of blood-culture studies in Chicago and Zurich, from those in Baltimore and Hamburg. However, in the absence of any experimental proof of such differences, such an explanation must be re-regarded as a mere speculation.

Nor can it be dismissed with the simple statement that improvement or recovery is necessarily associated with the absence or disappearance of the organisms from the blood. It is important to recognize that, although the pneumococci generally disappear from the blood before crisis, virulent organisms may be demonstrated in some cases even after the temperature has become normal. Yet it seems quite probable that the explanation may be found in some change (possibly a slight one) in the organisms themselves, produced perhaps by the antibodies, or defensive forces of the host. Experimental studies on pneumococcus infections in animals tend to show that the result of such infections depends on the balance acquired between the forces of the invader and the antibodies of the host, both of which may be present at the same time, as Mancini (14) has recently shown by the method of deviation of complement. Crisis or lysis will occur when the cause of the disease is overpowered by the resisting forces of the body, but, as Wolf maintains, without necessarily implying the death of pneumococci in the blood. Thus it is not difficult to conceive that in pneumonia the living organism might be present in the blood, but not always in such a condition as to grow when transferred to ordinary culture media.

We wish to acknowledge our indebtedness to Dr. Rufus Cole for valuable suggestions and actual assistance in the preparation of this report.

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MEMORIAL SERVICES FOR ISABEL HAMPTON ROBB, WHO DIED APRIL 15, 1910, AT CLEVELAND, OHIO.

A large number of the friends and associates of Isabel Hampton Robb assembled in the parlors of the Nurses' Home, at the Johns Hopkins Hospital, on Sunday afternoon, May 8, 1910, to do honor to her memory.

Remarks of Dr. Henry M. Hurd, Superintendent of the Johns Hopkins Hospital.

Several weeks ago, when we learned the sad news of the death of Mrs. Robb, there was a general feeling that we ought to take some immediate method of showing our appreciation of her work, and our great grief at her loss. It was thought best under the circumstances to have the simple service of the church that she loved so well. Accordingly, three weeks ago to-morrow a service wholly of a religious character was held in this room, which proved most comforting to all who were present. At that time, also, it was decided that as Mrs. Robb's work here had been of an epoch-making character and her memory was so dear to all, it was requisite we should have a more formal commemoration of her eminent services at this hospital, where she did the best and most enduring work of her career.

While sitting here I call to mind how on the 9th day of October, 1889, Miss Hampton, afterwards Mrs. Robb, made her first appearance in this room before a Baltimore audience, which had gathered at this time to signalize the opening of the training school for nurses connected with this hospital. Previous to that time the nursing work in this hospital had been carried on in a hand-to-mouth fashion, satisfactorily, upon the whole, as we had excellent nurses, but without special system. Each nurse had been trained in a different school and there was necessarily a lack of co-ordination and order. The hospital had been only partially opened and many important departments had not yet been organized; consequently up to this time it had not been possible to establish any training school. Miss Hampton came to Baltimore a few days prior to the first of October, but did not begin her duties as superintendent of nurses and principal of the training school until the date above mentioned. As the title indicates, she was not only superintendent of nurses, but also principal of the training school, and had charge of the education of the nurses, and her position as principal of the training school gave a recognition at once to the fact that she was engaged in the work of teaching.

I remember well the audience that gathered here on that October day to hear Mrs. Robb. There were Francis T. King, so many years the president of the board of trustees, to whom we owe this building, and who had very just ideas as to what proper nursing should be; also George W. Corner, who died only a short time ago, one of our oldest trustees; Judge George W. Dobbin, Judge Geo. William Brown, Dr. Alan P. Smith, C. J. M. Gwinn and Francis White, of the board of trustees. There were Lewis N. Hopkins, the nephew of Johns Hopkins; also Mrs. Miles White, his only surviving sister, and Henry D. Harvey, one of his business partners. There were President Gilman, Prof. Remsen, Cardinal Gibbons, Mayor Latrobe, Dr. James Carey Thomas and others. I might mention many others, but these will suffice to show the character of the audience present. Mr. King made an address, which was followed by a paper from Mrs. Robb, giving an outline of what she intended to accomplish in establishing the training school. In that paper she set a standard which has been adhered to ever since and which has had much to do with the success of the training school. What she said was so appropriate and gave such a good conception of what she wanted in a trained nurse, that I will read a few sentences:

> Schools for nurses, in fact, consider little that is sentimental and much that is practical, in deciding upon the fitness of a woman for nursing. While some may have more natural aptitude for the work than others, there are other attributes quite as important that are required.
>
> Training schools aim to receive only women who are at least fairly intellectual, the more so the better results, who are strong and enduring physically, and who morally will recognize the sacredness of the work that they are engaged in. Of their pupils training schools require that they shall yield implicit obedience and loyalty to the physician, that they shall faithfully carry out his directions, and in his absence watch over the welfare of his

patient, and further his scientific study of disease by intelligently fulfilling his orders in administering medicines, taking account of the range of pulse and temperature, regulating the sanitary condition of the sick room, noting every unusual symptom in the patient, keenly alive to its importance, and reporting the various changes in his condition, as the patient responds to treatment.

Thus by night or by day a nurse must be on the alert; she must have at her command presence of mind to meet any emergency, must abound in tact and patience with those suffering from mental disturbances, and be unwearying in her efforts for her patient's comfort; and all this and much more she must do cheerfully, being kind and sympathetic and adaptable to the varying necessities of the sick room.

I do not know but that this might have been expressed more concisely, but it certainly would not have given as fully Mrs. Robb's ideal of the true nurse and of the mission of the training school.

Mrs. Robb was with us for a period of five years. She brought order out of confusion and established a system of instruction which has gone on with increasing usefulness ever since she left us to marry in 1894. She did not give up her interest in the training school, but was always anxious to know of its welfare and prosperity. It was her conception of the teaching function of a training school which induced her to urge upon our trustees, even after she had left the school, the importance of establishing an eight-hour day, the importance of providing paid teachers and the importance of giving the pupils of the training school as much opportunity for study as they had for practical work. I think that these contributions to training school work were pre-eminently hers. She saw clearly the importance of giving instruction of a character suited to improve the intellectual capacity of the nurse, to increase her capacity for effective work, and finally to fit her to be not only a nurse but a teacher.

When she went to Cleveland, she showed a similar interest in hospital and training school affairs. I will, however, leave to others to give some account of her life there, as they know it much better than I do. Her personality commanded respect and affection. When you met her you were in contact with a generous nature and a personality with large ideas and broad views of her duty to the world and especially to the sick and suffering. I believe very few persons have ever been in this hospital who have left a better or more enduring impression. It is a pleasure to think of the women she trained: Miss Nutting, Miss Nevins, Miss Ross, Miss Barnard, Mrs. Thayer, Mrs. Finney and others. I could name many others, who worthily have carried on the work she began so ably and so nobly. We all owe a debt of gratitude to Mrs. Robb for her work and for the workers she has inspired.

I wish to ask Miss Nutting, as her successor, to give some account of her work and I would express the hope that she will speak at length.

Remarks of Adelaide Nutting, Professor of Hospital Economics, Teachers College, New York City.

I have been asked to speak to you this afternoon of the educational work of Isabel Robb, the great woman who organized this training school, established its standards, shaped its traditions, and placed it upon the basis educationally which has enabled it to hold for nearly twenty years a leading place among the great training schools of the world. That it has attained this high rank has not been due primarily, I believe, to the fact that it was connected with a hospital affording large and unusual opportunities, with costly buildings and elaborate equipment, and that we were connected with a noted university; other schools have these; but it has been due to Mrs. Robb's insistence from the beginning upon the importance of maintaining and developing the educational side of nursing work. At this moment we are too near her to give any just estimate of her work, and in this spot, so crowded with memories of her, it is difficult to speak at all, the more so, because, great as she was in her work, splendid as have been the influences and inspirations which have flowed from it, it is not at this moment the teacher, the organizer, the leader, whom we have lost and mourn, but the beloved woman, with her gracious ways, her radiant vitality and irresistible charm, her almost childlike delight in the beautiful and pleasant things of life, her warm human impulses, and even her human imperfections. For these things she is close to our hearts, and it is with an effort that we turn from them to pay tribute to her fine achievements through which alone in the future she will be known and honored, which are her imperishable contributions to the world.

I had the privilege of close and constant association with Mrs. Robb from my earliest days as a pupil in this school, and a friendship began then which has been one of the strongest influences of my life. Many times have we talked together of her home life and education, her training at Bellevue and her work in Chicago. Her upbringing was in a home of Spartan simplicity, and her mother, an English woman of the old school, had strong ideas of duty and discipline and of the part they played in the training of children. The daughter in the home had clearly defined duties and responsibilities, and Mrs. Robb often spoke of the value of the training in these very practical duties in her home, the performance of which was always rigidly insisted upon. She received on the whole an unusual education, remaining at school until about twenty years of age. She thought of teaching or of studying medicine, but the way did not seem to open, and eventually she entered Bellevue Training School, in New York, where she soon became intensely interested in nursing, discerning in it a work of great possibilities.

Upon her training in Bellevue Mrs. Robb frequently dwelt, and in teaching constantly drew for illustration upon the experiences which the hospital offered in such variety and abundance. The working day of the pupils ranged from 8 a. m. to 8 p. m. with, it was stated, one hour off for dinner, and "additional time for rest and exercise." Many conditions combined to make those hours off an uncertain and variable quantity. The wards were full of very sick patients, and the number of nurses to care for them small. There were many evenings, too, when the work could not be finished at the stated hour of 8 o'clock, and when her pupils remained on until a

later, sometimes much later hour, obtaining in some small shop in the vicinity the supper they had missed.

Attendance at lectures was not compulsory, if the needs of the patients were unusually urgent. The pupil could remain in the wards, or the head nurse could keep her there during lecture hour, and thus such theoretical instruction as was provided could be lost altogether.

Finally it came about that a little group of pupils, Mrs. Robb one of them, felt so greatly the need of further instruction that they gathered together in one of their rooms at night, after work was over, and carried out regular courses of study, as systematically arranged as the nature of their lives would permit. I remember particularly hearing Mrs. Robb speak of the regular classes and quizzes in anatomy and physiology which they tried to conduct, with the hope of acquiring a sounder knowledge of the human bodies they were caring for, in order that they might do more intelligent work over them. Often has Mrs. Robb assured me that her ideas as to the needs in the education of nurses grew out of her own experience, in finding herself confronted with conditions and situations in nursing for which little or nothing in her training had prepared her. Yet she never for a moment undervalued the kind of power which that training at Bellevue brought her, though she felt keenly the need of a sounder and better educational policy as a matter of justice to the pupil and to the work into which her hospital training inevitably led her.

I am inclined to think that at that time the pupils were sent out into private families during some part of their second year, for the stated purpose of acquiring experience not to be obtained in a municipal hospital.

On leaving Bellevue, Mrs. Robb spent a few weeks at the Woman's Hospital, and then joined other graduates of her school at St. Paul's House, in Rome, an institution established under the auspices of the American Episcopal Church, for the purpose of providing suitable nursing in illness for English and American visitors. I have often felt that here was her first contact with the beautiful things of the world, that the beauty and glory of life first dawned upon her in Italy. Over and over again in the evenings she would bring forth her cherished collection of photographs, and dwell upon the memories of her days there, as something very rare and precious which she had always with her.

At the end of a year and a half Mrs. Robb returned to America, and soon after went to Chicago, to take charge of the Illinois Training School for Nurses, connected with the Cook County Hospital, a very large municipal institution whose political control made conditions difficult to cope with. The training school was not, however, a part of the hospital, but was, and still is, under an independent body, a board of women managers. With their support, interesting developments were made in the work of the school.

Perhaps the first instance of an affiliation for an educational purpose was when this training school undertook to do the nursing in a large neighboring hospital—the Presbyterian—which offered in its private service additional and desirable opportunities for the pupil nurses. The lectures and other theoretical instruction in this school, as in most others at that time, had been limited to the first year, owing to the prevailing custom of sending pupils out into families to nurse during their second year. Mrs. Robb saw the advantages of continuing the instruction into the second year, and in carrying out this idea aimed unconsciously an effective blow at the common policy of sending out pupils.

Those who were associated with Mrs. Robb in Chicago very soon came under the influence of her wonderful personality, and to their admiration for her strong and progressive work, added a devotion which time and absence have not been able to impair.

In little less than four years the Johns Hopkins Hospital was completed and opening its doors and its training school, and from a number of candidates for the position of superintendent of nurses, Mrs. Robb was chosen. Here she found her great opportunity. Here was a new field, unmatched in its resources, rich in its possibilities, free from trammels of precedent or tradition, offering her freedom to work out her ideas and plans in an atmosphere sympathetic and helpful to an unusual degree, and here she did her greatest and best work.

From the very beginning she emphasized her desire to uphold educational ideals and standards in insisting that her title should be not only that of superintendent of nurses, but also principal of the training school. It is just a little pathetic to look back and remember that in the effort to give us as pupils some better instruction than was commonly offered in training schools, it was arranged that we should have two lectures a week of one hour each.

After a brief trial this had to be dropped; it was too advanced for the time. The lectures came in the evening, and while we could struggle through one in the week and work up our notes, two proved entirely impossible.

I have often heard Mrs. Robb speak of the diet school in a hospital as its one purely educational feature, in that the services the pupils might render to the hospital in it were the secondary, and not the primary, consideration.

While the opportunities were unusual, those first years of work presented many difficulties. In organizing the work it was necessary to bring in as heads of wards and other departments graduate nurses from various schools and from different countries. They not only differed widely in standards and ideals, but had been trained in methods so diverse that to produce a desirable uniformity or harmony in the system of training seemed well-nigh impossible. There were some excellent head nurses, women of fine powers and unswerving in their allegiance, yet it was no uncommon thing for us to be taught certain methods in the class-room by Mrs. Robb, and upon our return to the wards to find these methods questioned, and to be directed to use others.

To maintain unity and steadiness of purpose amidst the confusion wrought in the mind of the pupil by such conflicting influences required great patience and insight, and it has always seemed to me a striking evidence of Mrs. Robb's remarkable power that she was able to do it. I think few heads of schools have ever gathered about them a more devoted group

of pupils. We were filled with loyalty which could not be shaken. Constantly she held up to us the highest ideals in our work, placing before us unceasingly the importance of nursing and the great responsibilities which rested upon those who undertook it, urging that they must always be women of exceptional character and ability. She filled us with great pride in our work and a desire to contribute to its best development in all ways open to us. It seemed to us better worth doing than any other work in the world.

Notwithstanding the wide sweep of her vision, she was nevertheless one of the most practical of women. I have often been struck by the simplicity and the practical nature of her plans when they came to the sifting point. The measures she suggested were as a rule such as could be carried out. Sometimes they were large measures, but they were not often impracticable.

A noticeable feature of her character was her love of uniformity. I have often felt that there must have been a long line of military ancestry in the background to account for her ideas on this subject and on that of discipline. We were an army—we must work as an army—must keep step—must not get out of line—our standards must be uniform. It was, therefore, a matter of profound satisfaction when she was able to fill every post in the hospital and school with graduates whom she had trained, and could feel that a uniform system of teaching and training was established throughout the place.

At the end of five years Mrs. Robb had not only thus completed the organization of the work in school and hospital, but had during that period written and published her text-book of nursing—and then she left us.

In the fifteen years since that date, while still meeting fully the cares and responsibilities of home and family life and many large social demands, she steadily maintained her interest in nursing affairs, and her contributions to professional development have been noteworthy. As a member of the board of managers of Lakeside Hospital, she was happy in giving largely the results of her practical experience, and I have heard from the trustees and her co-workers there how greatly they relied upon her judgment and wisdom.

She was eager to see the development of a good system of visiting nursing in Cleveland, aided in its establishment, and was an enthusiastic supporter of its work, and I cannot think that she ever failed to respond in her own community to whatever call was made upon her in which nurses, hospitals, the care of the sick, or the prevention of sickness were concerned.

The Society of Superintendents of Training Schools owes its first impetus to her and the little group of seventeen heads of training schools with whom in Chicago in 1893 she discussed the formation of a society of such workers to advance educational standards and bring about uniformity of methods. That has now grown to a large society of 360 members.

Throughout all the years she has steadily attended the meetings and prepared papers, and only last year she was its president. The society about ten years ago appointed a committee of which she was chairman to study possibilities for the training of teachers of nursing, and the work of this committee eventually led to the establishment of courses at Teachers College, which have just grown into the dignity of a department —that of nursing and health.

Mrs. Robb was among the lecturers to the students of this course, and her last visit to New York, in January, was for the purpose of fulfilling such an engagement.

Of the Associated Alumnæ she was the first president, and carried it through its early difficult years of organization.

From the very beginning Mrs. Robb realized fully the value of the printed word, and her views, plans and suggestions were unfailingly embodied in some paper or report where they were, as she herself said, "on record." In addition to her two well-known books, "The Principles and Practice of Nursing" and "Nursing Ethics," which are in general use in training schools all over the country, there are among her writings several papers and addresses which I have long felt ought to be more widely available than they now are. I asked her last January if she would not soon gather together a collection of such writings, and from her reply I found that she was arranging for their publication, which we may hope will be soon. They will form an invaluable contribution to the literature of nursing, and we shall hold them among our most cherished possessions.

During the winter we have been preparing for a celebration of the Fiftieth Anniversary of the founding by Florence Nightingale of the first training school for nurses, and had asked Mrs. Robb, as one of our pioneer workers, to give an address on that occasion. She wrote, regretting that the pressure of many matters compelled her to decline, but as we were not willing to accept her refusal, after a few weeks I wrote again, begging her not to fail us. I had not heard from her when the appalling news of her death called me to Cleveland, but in talking with Dr. Robb, he told me of a few scattered notes which he had found in her desk, referring to nursing education under the title which we had named. So it seems that her last work for nurses was an effort to respond to our request that her voice and presence should not be lacking on an occasion of such unusual importance, and we know now that she was unwilling to fail us.

In all my knowledge of her I can hardly think of a time when questions of nursing were not uppermost and seemingly matters of vital interest. In her teachings, in her writings, in her practical contributions, and in her public activities she held up firmly and consistently ideals in nursing and in the education of nurses which compelled respect and attention and which in the general upbuilding of standards in a new field of women's work will be found ultimately to have been of quite incalculable value. Every year that passes will but add to our gratitude for her gifts and devotion to her memory.

Remarks of Mrs. William M. Ellicott, of Baltimore.

It is as my father's daughter, as well as the friend of the wonderful woman we have lost, that I would like to say a word this afternoon. It was my father's earnest desire that this training school for nurses should be a model in the United States, and I remember well his coming home one day and say-

ing, "I have found an administrator." Certainly we all know, from the fruitful results of Mrs. Robb's labors, that he had found an administrator; and from that time on it was one of his greatest pleasures to confer with her, and to listen to and encourage her admirable plans. She has often said to me, "I owe much to your father, because he appreciated all my efforts and always encouraged me;" and she nursed him so faithfully in his last illness that from that time on my friendship for her was so deep that I can harly speak of it now.

I feel that we cannot put a measure to the indebtedness which the profession of nursing owes to her; but I also feel that, as women, we owe much to her. Her type of womanhood was very remarkable: the serene look in her blue eyes told always of difficulties to be faced and conquered, never to be worried over, and whenever there was hard work to be done, she either went forward and accomplished it, or, if this were impossible, she laid it aside until it could be freely taken up again. Her example has made her the friend of all women, and we know that she has left behind her an ideal which, wherever we are working and wherever we are living, will be felt as the type of true womanhood. For her to have been snatched from us in her supreme vigor and maturity is perhaps to leave to us the most perfect memory of her; and I appreciate this opportunity to add a tribute to her from all the women of America.

Remarks of Dr. Lewellys F. Barker, Professor of Medicine, the Johns Hopkins University.

It is a very great privilege for me to be here and to be allowed to say a few words on this occasion. In the early years of my acquaintance with Mrs. Robb I had a very high regard for her, and as I learned to know her better that regard grew into a very strong friendship that increased with the years.

I want to speak about her death and burial. It is rather remarkable that her death should have been due to something quite out of accord with the main tenor of her life. Most of you have heard the details of that horrible accident in Cleveland, when, in a moment of curious indecision, she failed to cross the street and was caught between two cars and crushed to death. Usually easily able to decide promptly, she had for years had a sort of psychic indecision about that one matter of crossing the street; and she had spoken to many of her friends of her fear that she would sometime be killed by a street car. It is very remarkable that this psychic fear should have been well founded. Such an apprehension is almost never realized, but in this one instance unfortunately it was.

Mrs. Robb was Canadian born and was always most loyal to Canada and Great Britain, and although she did not expect to be buried in Canada she had often expressed the wish that this might be. After her death her husband, in order to carry out that wish, sent one of his best friends immediately to Canada to arrange for her burial in the spot which she had indicated; but unfortunately conditions were found to be unsuitable, and word was sent back strongly advising the postponement of the interment until better arrangements could be made. Dr. Robb himself then went to Canada and made an investigation personally, and felt so keenly the disadvantages of the local conditions that he appealed to some of us here, asking for advice and help. I talked with Dr. Hurd and with others about it, and we felt strongly that under the circumstances it was much better to have her interred at Burlington, New Jersey, her husband's home, where the conditions were very satisfactory and where her grave would be accessible to many, especially to nurses who might wish at some time to visit it. I mention this that those of you who may have been aware of her wish to be buried in Canada may know why that wish was not carried out.

I would like to say a few words about some of the qualities of mind and heart of her whose memory we are meeting to-day to honor. I think the first point that should be emphasized is her energy. The more I see of men and women the more I realize the importance of great energy well directed, and this Mrs. Robb had in superabundance. She gave the impression of the embodiment of energy. She did not easily show fatigue, and in her teaching work and her relations with others it was largely this force and activity in which she abounded that made her so strong and so helpful.

A second point is her enthusiasm. As Miss Nutting has emphasized, she was most enthusiastic in everything she undertook: for the time being it was her whole life. And she had the courage of her convictions. I have never known any woman more ready to stand boldly in the face of opposition for the point which she wished to make. As soon as she felt convinced that it was right she went ahead with it and fought for it, and it was not her fault if the point was not gained. But with her courage and enthusiasm there was always a deep sense of justice and right, and if she could be convinced that the thing which she had in mind was not for the best she was ready always to yield. In her dealings with nurses this faculty of justice was a noticeable one. Many nurses have said to me that they felt that Miss Hampton was always just, that though sometimes the decision seemed hard, there was always a good reason for it. Her sense of justice and right has been a matter of praise among all who knew her.

As to her relation to the training school I shall say very little—so much has been so well said by Dr. Hurd and Miss Nutting. I shall refer only to one point, and that is what she accomplished in raising the social status of the nurse. And this is a point which I think deserves emphasis, for I believe that largely through her influence—at first here, in the beginning of this training school—the social status of the nurse has been elevated to a very high degree throughout the whole country. When you think of the difficulties that stood in the way of a better class of women in training schools, when you think of the women she chose to be nurses and of those who have succeeded them ever since in this training school, when you think of the influence that such standards have had upon the choice of women in other training schools, then you will begin to realize that the social elevation of the trained nurse in America is one of the great contributions of Isabel Hampton. We of the medical profession appreciate this particularly,

because it has made it possible for the nurse to co-operate with the physician in a way which before had been entirely impossible. If a nurse is intelligent, refined and cultured and if she has charm, she can do for her patients something which is quite out of the power of one who does not possess these qualities. We realize this very keenly, and are always glad of an opportunity to point out this contribution which the Johns Hopkins Hospital Training School for Nurses, largely through the influence of its first superintendent, has made.

Another and a very pleasant side of Mrs. Robb which I had the opportunity of seeing, was as wife and mother. She has bequeathed to her two boys sound bodies and sound minds, and I am very glad that they have had her as an influence in their lives for at least as long a period as she was with them.

Hers is certainly one of the most notable personalities that the profession of nursing has offered to America and to the world; and these qualities that I have mentioned, of energy, enthusiasm, courage, justice and idealism, we may well keep in mind and carry away as lessons that her life has taught.

Remarks of Miss Georgia M. Nevins, Superintendent of the Garfield Hospital, Washington, D. C.

Just a word in behalf of that first class, and to mention a few points in Mrs. Robb's character that strongly impressed me all the years that we worked so closely together not only in the school, but since that time. If by any chance there is a feeling among the later pupils that the members of that first class have a very good opinion of themselves, it is far from true, for we realize that opportunities for the benefit of the pupils have increased every year over the advantages which we may have had; but it was a wonderful privilege to be under the direct and constant supervision of such a woman as Miss Hampton. She came here filled with enthusiasm and high ideals and soon selected the first class of seventeen. There was but one text-book for nurses at that time and all the teaching, practical and otherwise, was done by herself personally—only possible in those very early days of the hospital.

The quality of her work must have been indelibly impressed upon every one of her pupils. "The comfort of the patient" was emphasized always as our first consideration, and her faithful teaching of every detail of nursing has left an impression so vivid that, to this day, I rarely take a class without being reminded of her. Trained in Bellevue at a time when it was difficult to obtain the necessary comforts for patients, she developed a resourcefulness and knowledge of economy which proved most helpful to those of her pupils who later took charge of institutions less fortunately endowed than this. Her power of observation seemed very remarkable to young pupils. I remember one instance, when as a probationer, I had been told to put a room in order, which I thought I accomplished to perfection; Miss Hampton came into the room, and in a flash espied a tiny cobweb hanging from the chandelier, when, of course, my spirits fell. Another incident illustrates her intense interest in her work and its results. When I first took charge of the Garfield School, Miss Hampton came over frequently to see how her child was getting on. We had with us a graduate of this school on special duty. Miss Hampton came upon her in the corridor one day, and I am sorry to say that, without a cap and with her handkerchief carelessly worn instead of a collar, she did look rather untidy. A greeting over, the nurse passed on, when Miss Hampton's face flushed, her eyes filled with tears and she exclaimed: "Have I worked for this?" She was pained beyond description that her teaching was so soon forgotten.

Mrs. Robb's almost childlike interest and enthusiasm in so many different ways was truly remarkable. Within one hour I have known her to be absorbed in the outline of the new preliminary course which we were to take up in the school, and in the next, she was just as interested in sewing lace on a baby's dress. Rarely is a woman endowed with such superb physical strength and great dignity. We found her very firm, upon occasion, but always eager, full of the joy of living, and we can never forget her fascinating smile and the gentle voice which it is impossible to believe is forever still.

I have been asked to speak of Mrs. Robb's work in connection with the Red Cross. She was interested from the beginning of the Red Cross reorganization, and wished to see a large enrollment of the best nurses of the country, to be called upon in the event of war or other emergency needing their services. She was asked by the Red Cross Central Committee to outline a system of enrollment. This she did, and while her plan could not be carried out altogether, on account of the expense, it led to the present organization through the State and local associations of graduate nurses.

One word more: We may hold meetings in her honor, portraits may be painted, but it seems to me that there can be no monument to Mrs. Robb equal to the influence in the world by the graduates of this school, if we carry out the principles and ideals of our first superintendent, Isabel Hampton Robb.

Remarks of Dr. William H. Welch, Professor of Pathology, the Johns Hopkins University.

I am sure that everything possible has been said to indicate our esteem and appreciation of Mrs. Robb's work. There is only one other point that perhaps may need to be emphasized. If there is one thing more than another distinctive of the medical work in this place it is that all the forces concerned have worked together as a unit—the university, the hospital, the medical school and the training school for nurses. The influence which has been attained is due in very large measure to this co-ordination and harmony, and I regard the work of the training school as one of the most important contributions of this place, from the medical side, to the country. The interest which attaches to Mrs. Robb's association with the work is that kind of interest which always goes to a pioneer, to the one who has begun things which have become important; and her name, therefore, will always be a name to be treasured, not only here, but throughout the country.

I perhaps knew Mrs. Robb slightly earlier than anyone here, as I was one of the lecturers to those hard-worked nurses at the

Bellevue Hospital. I recall very vividly going down in the early days to the Bellevue Training School at half-past eight at night, and those weary, tired nurses coming in and sitting in a row for me to talk to for an hour. I used to welcome their nodding heads, for I felt that then at least I was doing some good. Mrs. Robb has herself occasionally referred to this experience.

Now the Bellevue Training School was, of course, a pioneer in the work of nursing in this country, but Miss Nutting, in her very interesting and admirable survey, has pointed out in what respects it was defective—especially in the long hours and the very meager character of the educational side of the work. Therefore, I may speak for all of my colleagues in the medical school when I say that we are very proud of our training school and that we are very proud of those who have made it such a success. It stands, in its own sphere, toward the profession of nursing as eminently as the medical school and the hospital do in their respective provinces. Now one must have some understanding of the value of the profession of nursing in modern medicine to appreciate how significant and important a contribution it is in the whole field of medicine and also to the community at large. It has changed the face of modern medicine; it is revolutionary in its influence upon the progress of modern medicine. We can hardly imagine ourselves back in the days when the trained nurse did not exist, but we can imagine what a backwoods, and even medieval, state we would be thrown into if we had not this great arm of medicine to lean upon. Commensurate in importance are the problems connected with the education of the nurse, for they are not all settled to-day. They are large problems; and hence the work of one who contributes to them is a large and important work. Mrs. Robb, therefore, did not work in a small corner; hers was not work relating to a very restricted and limited field; but it was work which pertains to one of the most important developments in medicine, and indeed in social reform, of the day.

Miss Nutting has admirably indicated the general features of Mrs. Robb's work here in the training school, and I shall, therefore, only point out that the hospital was most fortunate in securing her services. She proved to be the one best adapted to initiate and carry on this work, by her forceful, charming and attractive personality and by her excellent qualities of mind and heart. We were, therefore, singularly favored in having her with us at the beginning of the training school. Her work marked a very important era in development. It has stood, and stands to-day, for certain ideals—ideals which are not universally accepted by others—ideals that there is no such thing really as over-education of the nurse, but that a nurse—as Dr. Barker has so well pointed out—is all the more of service the better her general education and her qualities of heart and of character. These are, in part at least, the ideals which I think we may say that the training school of the Johns Hopkins Hospital has introduced.

Those of us who were here in the beginning when the hospital was opened count Mrs. Robb among the group who started things here, and I venture to say that as long as this hospital endures her name and her work will be among its most cherished possessions.

Isabel Adams Hampton Robb was born at Welland, Canada, in 1860. She received her education at the Collegiate Institute, St. Catherine's, Canada, and in 1881 entered the Training School for Nurses connected with Bellevue Hospital, New York, and was graduated from there in 1883.

Following her graduation, Miss Hampton spent a short time in private nursing, and was then appointed Head Nurse in the Woman's Hospital of New York City. She resigned this position to go to Italy, where for nearly two years she nursed in connection with St. Paul's House for Trained Nurses in Rome.

In July, 1876, she was appointed Superintendent of the Illinois Training School for Nurses associated with the Cook County Hospital in Chicago. During the three years of her service there she brought about the affiliation of the Presbyterian Hospital with the Cook County Hospital in the matter of nurses and made notable improvements in the method of training nurses.

When the Johns Hopkins Hospital was opened Miss Hampton was chosen as Superintendent of Nurses and Principal of the Training School for Nurses and entered upon her duties October 1, 1889.

In May, 1894, Miss Hampton resigned her position at the Johns Hopkins Hospital and in the following month was married at St. Margaret's Church, Westminster, London, to Dr. Hunter Robb, formerly of Baltimore. In November of the same year Dr. and Mrs. Robb went to reside at Cleveland, Ohio, and there their two sons, Hampton and Philip, were born.

In Cleveland she maintained an active part in nursing affairs and became a member of the Board of Lady Managers and Chairman of the Training School Committee of the Lakeside Hospital.

She was also the promoter of two prominent nursing organizations in this country, "The Society of Superintendents of Training Schools," and "The Associated Alumnae of Trained Nurses," and was instrumental in founding "The American Journal of Nursing." The course in Hospital Economics in the Teachers' College, Columbia University, was largely the outcome of her efforts.

In recognition of her work in presenting the need of well-trained nurses to the Red Cross Society, she was made a member of the War Relief Board of the National Red Cross Society. She was also a member of the Matron's Council, London, England, and was appointed delegate to the last International Congress of Nurses.

In addition to numerous papers and addresses, Mrs. Robb was the author of three books: "Nursing, its Principles and Practice, 1894"; "Nursing Ethics, 1900"; "Educational Standards for Nurses, 1907."

IN MEMORIAM.

CAMILLUS BUSH.

On Saturday, May 28, 1910, Dr. Camillus Bush, of the class of 1902, Johns Hopkins Medical School, died at the Adler Sanitarium in San Francisco. He had been ill for about three weeks, suffering from typhoid fever; but a double pneumonia, which developed during the third week, was the immediate cause of death. He was buried at his home in Woodland, California.

Those who knew Camillus Bush in Baltimore have felt that their appreciation of his rather unusual traits of character should receive some adequate public expression, and have desired to record their feelings in The Johns Hopkins Hospital Bulletin.

We should be untrue to his memory if our affection for him should lead us into any extravagant estimate of his worth; for he fled from flattery; and while he was quick to recognize real excellence in others, he was always discriminating in praise and frank in criticism. The attitude of sincerity which he maintained toward others, he was glad to have others maintain toward himself.

He came to this Medical School from the University of California; and he brought with him the rugged virtues of pioneer ancestors. From the first he shunned publicity, but his quick mind and ingratiating ways soon made of him a marked man. He made many and strong friends in the Medical School and in the city. His few antagonisms were equally strong and equally creditable to him. To his medical work he gave intelligence and devotion. The facility with which he absorbed information, and the ease with which he acquired skill were the admiration and envy of those who worked with him.

His service in the Johns Hopkins Hospital as interne and as Assistant Resident Surgeon fulfilled the promise of his student days. His chief interest was always in the clinical side of medicine; and his hospital days first gave him the opportunity for the exhibition of easy, but faithful, acceptance of responsibility, tactful and thoughtful care of patients, keen surgical insight and excellent surgical judgment which promised so much for his success as a surgeon. When Bush left Baltimore the affection of every one with whom he had come in contact went with him; and it is well within the limits of moderation to say that no one who has served the Hospital has been more widely loved than he.

In San Francisco he met with unusual success. In spite of great discouragements at the first—emphasized by his undaunted devotion to high ideals which refused to accept compromise that would have made progress easy—in spite of a somewhat uncongenial medical atmosphere, he rapidly forged to the front; and though only 32 years of age, and but 8 years in practice, he was at the time of his death one of the most promising young surgeons of his city: competing, and competing successfully, with men of years and experience, and widely admired and respected by the profession.

He was a man of unusual integrity. His professional conscience was like a knife-edge. He saw with a keen eye the daily petty compromises with ideals which longing for success forced men around him to make; but no such compromises, not even the most trivial, entered into his own programme of life. Indeed, those who were interested in his early San Francisco days rather feared that he might be over-doing his assertion of independence; but his candor and honesty finally won for him the respect of the profession; and though he never made any efforts—not even the most respectable—to force a practice, patients, and patients in good numbers, soon found him out and sought his aid.

He was a man, too, of unusual ability. Things came easily to him; and this facility almost led him at times to an intolerant attitude toward those who found difficulty in their work. But he was quick to discern and generous to praise excellence in others. He felt no particular call to the productive side of research in medicine; but he was keenly alive to all that was being done in this direction. He set an excellent example by keeping out of work for which he did not feel himself fitted, and by maintaining an attitude of intense and freely expressed disgust for the pseudo-scientists who interpret research as self-exploitation. He was an excellent operator, had sane surgical judgment, understood the sympathetic care of patients and accepted his work with a due sense of responsibility.

He was a man of unusual charm. His outlook on life was fresh and boyish, his fondness for life deep and his belief in its essential excellence strong. His alert mind, ready wit, shrewd eye for human frailties, whimsical way of putting things and constant cheerfulness made him the very best of companions. He not only enjoyed life himself, but was the cause of its enjoyment in others. These excellences of his character were by no means casual. They were the expressions of a nature essentially serious, essentially spiritual—for Bush had a faith almost naive in its intolerance of doubt, a faith for which "all sorts of proof were impertinent"; and many who had seen only the fun-loving, lighter side of his nature would be surprised if they knew to what an extent this belief shaped and dominated his career and what sacrifices he made for it.

Men of Bush's type are not born every day. The city where he worked and the profession which he served need such men. Those who have known the delight of intimacy with him, mourn him with a deep and sincere sense of personal loss.

J. W. C.

THE JOHNS HOPKINS HOSPITAL BULLETIN.

The Hospital Bulletin contains details of hospital and dispensary practice, abstracts of papers read, and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly.

Volume XXI is in progress. The subscription price is $2.00 per year in the United States, Canada, and Mexico; foreign subscriptions $2.50.

PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS MEDICAL SOCIETY.

March 21, 1910.

Dr. Louis Hamman presiding.

I. The Effect of Diminished Blood Supply to the Intestines upon the General Circulation. Dr. W. T. Longcope, Philadelphia, Pa.

To be reported in full in the September number of the Johns Hopkins Hospital Bulletin.

II. The Morphological Reaction of Certain Nerve Cells in Functional Activity in Relation to Surgical Shock.[1] Dr. D. H. Dolley, Chapel Hill, N. C.

The changes in size and in the nucleus-plasma relation in the Purkinje cells formed the basis of discussion. The sequence of the changes in chromatin content, previously published in a paper by Dr. Dolley, was summarized to show the correlation with the size changes. The findings were based on the measurements of two thousand two hundred cells and nuclei. The material came from five dogs, one normal, one exercised in a treadmill, and three shocked to death by intestinal manipulation. The use of three fixatives to control the results divided the data into eight series. In each series, the chromatin changes were separated into eleven main, and subsidiary stages, so far as they appeared according to the severity of the experiment, and the figures and curves presented were based upon the average for the most part of twenty-five cells to each of these stages, though in one case fifty, and in the normal seventy-five were taken. The sizes were calculated in actual volume figures.

With the transition to activity, the size of both cells and nuclei increases along with the progressive hyperchromatism. Before the maximum hyperchromatism is reached, the size begins to diminish, and with the regressive hyperchromatism declines through the shrunken cells first depicted by Hodge. From this minimum, the size of both elements increases with the onset of edema to the last stage measured in which the karyosome alone remains of basic chromatin.

The nucleus-plasma relation remains constant up to the maximum of enlargement with hyperchromatism. In the light of the work of Hertwig and his associates, this finding was regarded as very significant in delimiting strictly normal activity. The size of both elements increases but in the same ratio. From this point, the nucleus decreases relatively more, so that the relation comes to be progressively in favor of the cytoplasm. The onset of edema in the nucleus before the cytoplasm brings about a shift in the relation in favor of the nucleus, which reaches its maximum at the point where the cell is passing through the semblance of normal in its chromatin reduction.

Then the factor of edema in the cytoplasm begins to turn the balance the other way and to the end the relation is progressively in favor of the cytoplasm.

From these facts deductions were made regarding the mechanics of nerve-cell activity, bringing the changes in size and chromatin into relation. The hyperchromatism was explained as being a disturbance of the equilibrium in favor of chromatin formation, an initial overactivity on the part of the nucleus. When, however, the consumption of extra-nuclear chromatin comes to exceed its formation, there results a functional hypertrophy in the relatively more strained nucleus, so that the relation comes to be volumetrically in favor of the nucleus.

This accords with Hertwig's idea that the result of functional activity is first a disturbance of the balance in favor of the nucleus, for in the stage of hyperchromatism the nucleus is to be judged by the external measure of its activity in extra-nuclear chromatin. Following the nucleus, the cytoplasm becomes hypertrophic, and the visible result of the enlargement of both is the secondary outpouring of chromatin which follows the exhaustion after the onset of fatigue. Finally as a result of the increased demand on the part of the cytoplasm, depending on the greater diminution of nuclear activity, the relation comes to be disturbed in favor of the cytoplasm, and the natural limit is reached in actual dechromatinization of the nucleus.

In conclusion, from the inherent significance of a purposeful character in the changes, from the analogy with an obviously physiological condition such as muscular exertion, from the practical application to various functional states shown by differential counts, and from the agreement with accepted manifestations of activity, the changes are held to be the morphological expression of functional activity in the type of cell considered. In the case of such shock as was experimentally induced, its effects appear to be essentially the manifestation of varied states of activity, overactivity, fatigue and exhaustion in nerve cells. The symptomatic expressions are to be referred to the degree of the reaction and to its manner of localization.

April 4, 1910.

Dr. Louis Hamman presiding.

I. Disturbances of Peripheral Cardiac Innervation in Acute Infectious Diseases. Dr. C. F. Hoover, Cleveland, Ohio.

Dr. Hoover reviewed several observations made by himself and his colleagues on the alteration of heart-rate and blood-pressure as a result of pressure on the vagus nerve. In one or two instances this pressure was digital and made by the observer and the characteristic changes in the pulse-rate and blood-pressure were noted. In the remainder of the cases the pressure was brought to bear on the intra-thoracic portion of the vagus by pathological processes involving the mediastinal glandular tissue and the lungs themselves.

One case in particular, which was confirmed by autopsy

[1] To appear in full, under the title "The Pathological Cytology of Surgical Shock," in the Journal of Medical Research, XXII, No. 2.

showed the effects of pressure on the vagi. This case was that of a young girl, aged 12 years, who for several months had paroxysmal attacks of asthma. These attacks were of very short duration and during the intervals between attacks, the patient suffered no embarassment of the respiratory or circulatory system.

During one of these attacks the patient died and at autopsy, a large mass of caseous tuberculous glands was found in the thorax and running through the midst of these glands both the vagi and the phrenic nerves were found.

The second case reported was a remarkable one of arterial hypertension. This patient, a woman of 40 years, had been suffering with angina for over 15 years and when admitted to the hospital showed a blood-pressure (radial) of 350 mm. of mercury. Marked difference was made out in the blood-pressure in the femorals as compared with that in the radial arteries. There was no enlargement of the heart and the patient did not experience any pain on percussion at the edge of the area of cardiac dulness which Dr. Hoover believes to be present in cases of early cardio-vascular disease.

There was no fall in blood-pressure evident, when patient was asleep.

II. Multiple Carcinomata Arising from the Branchial Cleft and their Differential Diagnoses from other Malignant Lesions in the Neck. Dr. J. C. Bloodgood.

Carcinomatous growths in the neck, with certain restrictions represent a favorable and curable form of carcinoma. Unfortunately the great difficulty in these cases lies in the apparent inability of the physician to convince the laity that an early surgical intervention is possible. In the great majority of cases the patients come into the surgeon's hand at a stage, too late for surgical measures.

In nineteen cases of multiple carcinomata arising from the branchial cleft, studied both from a clinical and surgical aspect, the following interesting facts have been noted:

Only two cases occurred in individuals under 40 years of age. The remainder of the cases were in patients between 40 and 70 years of age. In but two exceptions the duration was less than two years.

The principal symptom of onset was that of a "palpable and movable tumor in the neck." Pain served as an early symptom in but few of the cases. Stiffness of the neck was the most common complaint. No etiological factor seems evident, trauma was offered in but one of the cases, while the "extraction of a tooth" was thought to be the causal factor in another case. This form of tumor may have the same situation as a benign atheromatous cyst. It is important to keep in mind that growths in the neck presenting redness, swelling and abscess formation may be one of carcinoma formation, which have broken down.

April 18, 1910.

Dr. Rupert Norton presiding.

I. Recent Views on the Production and Destruction of Uric Acid in the Animal Body. Dr. Walter Jones.

See third article in this number of the Bulletin.

II. Report of Pathological Specimens. Dr. E. K. Cullen.

Dr. E. K. Cullen reported a series of gynecological cases and exhibited drawings and pathological specimens.

Case I.—*Combined adenocarcinoma and mixed-cell sarcoma of the ovary.*—This tumor occurred in an unmarried woman fifty years of age. The tumor originated from the left ovary. It measured 15 x 14 x 7 cm. On gross examination it presented a definitely malignant appearance. On section of the tumor it was impossible to state whether the growth was a carcinoma or a sarcoma; for in some places it resembled the former, while in others it showed a typical picture of the latter. On microscopic examination it was found to be a mixed tumor, showing a definite adenocarcinoma with a stroma of mixed cell sarcoma. In some areas the carcinomatous process was more prominent, while in others only a few atypical glands were seen in a mass of typical sarcomatous tissue. Such tumors occurring in other organs (uterus and thyroid) have been reported, but a careful search of the literature for a similar tumor of the ovary was unsuccessful. There were no metastases found at operation. At the present time, however, some months after operation, the patient shows signs of local recurrence.

Cases 2 and 3.—*Sarcomatous transformation of myomata.*—These two cases showed early sarcomatous change in myomata. In Case 2, the change was so early that it was overlooked on gross examination.

Case 4.—*Extensive adenocarcinoma of the body of the uterus; myomata uteri; tuberculosis of the left Fallopian tube; and parovarian cyst on the left side.*—This case was especially interesting on account of the multiplicity of pathological processes present. The association of the carcinomatous and tuberculous processes is especially interesting. Careful examination of the stroma of the carcinoma adjacent to the tube showed no evidence of tuberculosis.

Case 5.—*Primary carcinoma of the appendix.*—The history of this case was that of chronic appendicitis. The appendix was 9 cm. in length and averaged 9 mm. in diameter. There was definite thickening of the distal third of the appendix, and on section the lumen was found to be almost obliterated. Malignancy was not suspected on macroscopic examination. On microscopic examination, however, a section taken through the appendix close to the tip showed a definite adenocarcinoma which involved almost the entire thickness of the wall.

Serial sections were made, and it was found that at the tip the carcinomatous process involved the entire wall, but at no point did it penetrate the mesentery. As one approached the central portion of the appendix, however, the process became limited to the mucosa and the lumen. Sections taken from the central and proximal portions of the appendix showed only slight round-celled infiltration of the submucosa.

May 16, 1910.

Dr. Rupert Norton presiding.

I. Experimental and Clinical Illustrations of Dyspituarism. Drs. H. Cushing and E. Goetsch.

For a full discussion of these experiments the reader is referred to a paper under title of Experimental Hypophysectomy in Bulletin of The Johns Hopkins Hospital, May, 1910, Vol. XXI, No. 230.

II. On the Action of Various Antimony and Arsenical Compounds in Experimental Trypanosomiasis. Drs. J. J. Abel and L. G. Rowntree.

Some sixty different varieties of trypanosomes have been found up to the present time and almost as many supposed remedies for this disease have been claimed by their respective discoverers.

In the main those compounds showing trypanosomicidal virtues are compounds of arsenic and antimony. Since the introduction of the "atoxyl" compound by Thomas, this substance has been tried with countless changes and modifications. The term "atoxyl" seems misleading, since certain toxic effects and untoward symptoms have been noted after long continued use of this drug. The antimony compounds appear to be much less toxic in their action than the arsenic compounds. Dr. Abel finds that it is easy to cure small animals, such as rats, in experimental infections of trypanosomiasis. Treatment must be begun soon after infection has taken place.

Protection against the disease seems absolute when the drug is given at the time of the inoculation of the animal. Twenty-four hours after an intra-peritoneal inoculation of the animal, the course of the disease may be stopped by the giving of the drug. Even at the end of three days (72-78 hours) after inoculation, at which time the animal usually succumbs to the disease, administration of the drug causes a prompt recovery. Relapses may occur, but these cases promptly respond to treatment. Of 104 rats, all of which received an experimental infection, 41 are still living and a large number of those dying were undoubtedly killed by overdosing at an early stage in the experiments when the proper size of the dose had not as yet been established.

But few experiments have been tried on the other laboratory animals, such as dogs and cats, and much work has still to be done along these lines.

III. The Toxicology of the Tutu Plant. Dr. W. W. Ford.

Tutin, tutu, or the toot poison is the active principle of several species of Coriarieæ, a group of plants found especially in New Zealand. On account of the serious pecuniary loss through the many deaths which occur in stock from eating these species, this plant has received much attention of late years.

The Coriarieæ are small shrubs or small trees and both their succulent branches and delicious berries are eaten with avidity by the domestic animals. The native Maoris have been familiar with the poisonous character of these plants since early times and from their language the term "toot" or "tutu" is derived.

The various species of Coriarieæ are identical in their poisonous action and no animal is naturally immune. Cattle and sheep especially suffer most severely, but larger animals are also susceptible. Owing to the widespread knowledge of the deadly character of the plant and its ease of recognition the number of cases on record of poisoning in man is not large, perhaps some twenty to twenty-five in all.

In animals poisoned by the plants the symptoms are largely referable to the nerve centers and consist of increased respirations, tetanic convulsions and coma. These symptoms usually make their appearance within a short time after eating and lead to death of the animal in a few hours. In man recovery from severe poisoning occurs, but impairment of memory may result. Very many remedies have been tried but without marked success. Bleeding is a therapeutic procedure which has received much favor by the stock owners and in cases of poisoning in human beings this has been combined with the use of stimulants, emetics, compulsory exercises and chloroform to control the convulsions. Lime, carbonate of ammonia, and other alkalis have proven effective remedies in the hands of some of the investigators.

"Tutu" the active principle may be obtained from the juice expressed from the finely divided young shoots of the plants. After filtration and evaporation to a thick syrup, it is then neutralized by sodium bicarbonate and a crystalline deposit is obtained upon recrystallization; the crystals are colorless, odorless and in shape oblique-ended prisms. The compound is volatile, has an intense and lasting bitter taste and gives the chemical reaction of a glucoside. That is it reduces Fehling's solution only after inversion by mineral acids, but then very strongly. It has the percentage composition of $C_{17}H_{20}O_7$. It is highly toxic, 0.129 gram killing a pig weighing 17 kilos in 5 hours, 0.01 gram killing a kitten weighing 1 kilo in 40 minutes and 1 milligram causing a severe illness with convulsions in a cat of average weight.

Dr. Ford has subjected this compound to many exhaustive tests and has ascertained the following additional interesting facts. Tutu is a poisonous crystalline compound to which immunity cannot be produced. It is itself very resistant, it can be boiled without destruction and must be hydrolized with strong acids before it gives off its sugar molecule. In its resistance to heat it may be compared to some of the snake venoms.

Tutin solutions preserve their toxicity for long periods of time without apparent deterioration.

In animals dead from tutin intoxication it is possible to locate the poison accurately in the nerve structures to which it is closely bound. The poison may be identified by its chemical reactions.

THE LÆNNEC SOCIETY.

March 31, 1910.

Dr. Rupert Norton presiding.

I. Intra-thoracic Displacements in Pulmonary Tuberculosis. Dr. Albert P. Francine, Philadelphia.

See second article in this number of the Bulletin.

II. Demonstrations of X-ray Findings in Pulmonary Tuberculosis. Dr. Charles L. Leonard, Philadelphia.

The study of pulmonary tuberculosis by the Roentgen rays has extended over most of the period since their discovery. The air-filled lungs showed in marked contrast to the sur-

rounding structures upon the fluorescent screen. In consequence the fluoroscope was first employed in the study of pulmonary tuberculosis. With it more rapid progress could be made because at that time viscera in motion could be observed that could not be roentgenographed.

Roentgenoscopy has, however, never afforded more than a rough method of visually confirming the findings of other methods of physical diagnosis. It lacks the essential elements of clear detail and mechanical registration which give accuracy to the roentgenogram. It yields visual, fleeting images that can only be compared mentally with the normal or other pathologic images.

The roentgenogram made while the patient held the breath showed the fallacies of the roentgenoscopic method. The instantaneous roentgenogram by eliminating all motion has rendered the fluoroscope valueless, or only of slight secondary importance, so that it is being abandoned by its most ardent advocates, and only used where the number of examinations make accuracy of secondary importance to the time and expenses incurred.

Improvements in apparatus and advances in technic have made possible exposures of one-fourth of a second and less, and have thus eliminated the motion due to the heart's pulsations. Stereo-roentgenograms made with these short exposures possess a detail and give a power of observation that render roentgenoscopic observations crude and valueless.

The advance to instantaneous stereo-roentgenography affords an opportunity of observing the pathological changes in the tuberculous lung, that is limited in value, only by the ability of the observer to differentiate the pathological from the normal. It gives, by mechanically registering the changes present, the opportunity for study, by numerous observers, of any one case; the repeated comparison of each case with the normal, with other pathological findings in other cases, and with other observations of the same case.

The value of this method is therefore dependent upon the ability of the observers to translate what is to be clearly seen. As in all other methods of diagnosis, the personal equation enters and the value of the diagnosis must depend upon the ability of the observers to translate the facts elicited. This method, however, possesses the advantage that the data secured are mechanically registered and can be submitted to any number of observers.

It compares favorably with a microscopic section or pathological specimen, and has the advantage, for the patient, that it is antemortem evidence.

The Roentgen method of examination can only show macroscopic lesions, which are recognizable as variations from the normal. It can in no way suggest their etiology. Since it cannot determine the cause it can only be used to suggest, confirm, amplify and render more accurate and permanent the findings of other methods of physical diagnosis. This method will often show lesions which cannot be determined by the physical signs but are suggested by the symptom-complex. It will determine more accurately the position and extent of all macroscopic lesions. Thus enlarged peribronchial glands and deeply situated areas of infiltration and consolidation can be shown which cannot be recognized by other methods of physical diagnosis.

Although this method by itself is incapable of establishing an early diagnosis of pulmonary tuberculosis, it often adds definite evidence of pathological change to a clinical picture which lacked confirmation by physical signs. It thus assists in forming an earlier diagnosis than could have been made without it.

In the later stages of the disease it gives more accurate information regarding the size and position of areas of infiltration, consolidation, softening and cavitation, while outside the lungs it localizes areas of pleural effusion or of pneumothorax. It is particularly with reference to the changes in position of the heart and greater blood-vessels that this method has produced an increase in our knowledge. The relative height of the two sides of the diaphragm has played a prominent rôle in the fluoroscopic study of pulmonary tuberculosis. The study of the positions and displacements of the mediastinal viscera shows that the changes in their position affect the relative capacity of the two lungs more than the variations of the diaphragm.

The presence of early adhesions of the pleura and pericardium to the diaphragm have been shown, with variations in the position of the heart causing rotations upon its axis until an antero-posterior position has been reached, or marked dextro-cardia with, in extreme cases, a displacement of the entire aorta with the heart.

Another pathological change frequently noted has been the calcification of the costal cartilages. The connection between this change and pulmonary tuberculosis has not been demonstrated, but the question arises is it the result of limited motion, or as the author has suggested in a previous paper, possibly a process of anchylosis to limit motion, such as accompanies tuberculous arthritis.

In the stereo-roentgenogram more minute detail can be perceived. The size, form and relation of infiltrated areas to the cavities which they surround is defined more clearly in three dimensions. More minute glands can be distinctly seen as glands; dilated bronchi can be noted, and the displacements of the viscera readily estimated with the adhesions which occasion them.

In the lantern slides which follow and the negatives as shown in the stereoscopes will be seen the demonstration of the points summarized above.

III. Influence of Menstruation on the Course of Pulmonary Tuberculosis. Dr. David I. Macht.

This paper will appear in full in a later number of the Bulletin.

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CONTENTS.

THE USE OF THE X-RAY IN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS.*

By Charles L. Minor, M. D., Asheville, N. C.

It was with great pleasure that I received an invitation to address you to-night, for clinical medicine and physical diagnostic methods are deeply interesting to me, and if I may judge by the illustrious name which your society bears, such are the chief objects of your study. Interesting to the physician as are therapeutic problems, diagnostic ones are, I believe, even more so, and, indeed, the latter can alone form a rational foundation for the former.

To the thoughtful mind the search for hidden truth must always be alluring, and the process of reasoning by which we arrive at a diagnosis is a delightful mental discipline and exercise. Hence, *causas morborum cognoscere* will always be the physician's watchword, not only because thereby he can better relieve sickness and suffering, but almost as much for the pure joy of knowing the truth.

Animated thus by a keen interest in every method which promises to reveal new truth the profession have been deeply interested in the diagnostic use of the Roentgen ray ever since the discovery of its ability to transluminate the body and reveal to us the condition of otherwise hidden organs, and physicians have hoped by its aid to attain with less danger to that certainty which our surgical brethren seek for (but do not always find) when they supplement their diagnostic skill by the knife, which lays bare to their physical eyes those cavities whose condition they have sought to discover with their mental vision.

It is but a few years since Prof. Roentgen discovered the rays that bear his name, but all over the world physicians have been studying its application to medical diagnosis, and have already greatly enriched our art and science thereby.

To no part of the body is it more applicable than to the thorax. None is so easily penetrated by the ray, none contains organs of such vital importance, or whose diseases make such frequent demands on our diagnostic skill, and it is therefore no wonder that students of the diseases of the lungs, despite the costly and cumbersome apparatus, have looked to it for new light upon the problems with which they deal.

At the same time this very cumbersomeness and cost have

* Read at a meeting of the Lænnec Society of the Johns Hopkins Hospital, February 28, 1910.

retarded its general adoption by the profession, and only in large hospitals and by a relatively few specialists in X-ray work, or in pulmonary diseases, has it been in sufficiently constant use to allow of drawing conclusions as to its utility in everyday diagnostic work.

Hence, when I was asked to speak to-night to this society, which is connected with a medical school justly celebrated for its diagnosticians, a society composed of men all of whom are deeply interested, and constantly busy, with diagnostic problems, I felt that it would be appropriate to speak to you of the use of the X-ray in the diagnosis of pulmonary tuberculosis. Having used the fluoroscope daily in all my pulmonary diagnostic work for the past ten years, I have been able, in the first place, to master its technique, and, secondly, to form definite impressions as to its utility and limitations, and possibly my views on these subjects may be of interest to you.

In our large hospitals where there is an expert in charge of the apparatus, or in the office of the especially equipped X-ray specialist, radiography, or photography with the X-ray, has, as you all know, been rendering valuable service for a number of years, its claims are recognized and it has come to stay, so I shall not here enter into this phase of the subject, being satisfied that my audience does not need to be convinced of its value, having seen the skilled work in this line done in the Johns Hopkins Hospital.

What is interesting the profession to-day is the question as to whether the X-ray is applicable in the private work of the physician, either specialist in lung diseases or general practitioner.

All over this land are many men ready to spend money, and a smaller number willing to give time, to master this new diagnostic art, if only they can feel sure that it offers them a really practical aid in the study and treatment of their cases of lung trouble.

Having, as a general practitioner, and as one interesting himself especially with pulmonary troubles, used it extensively, I may be able to throw some light on this question.

The satisfaction which a physician will get from the use of the X-ray in his private work depends, then, on three things; first, the frequency with which he makes use of it, or, in other words, his thorough familiarity with the apparatus, second, the kind of equipment he gets for it, and third, the form (fluoroscope or radiograph) in which he uses it.

As to the frequency of its use, just as no one would expect the doctor who only uses percussion or auscultation at long and irregular intervals to be able to properly master their intricacies, so with the X-ray, the doctor who expects to master it and get valuable aid from it must make use of it daily and systematically. He who only expects to look at an occasional case will derive no benefit from it and will soon give it up in disgust, since he will never reach the point when he will see with it easily and clearly, or be able to interpret his findings correctly. Therefore, the general practitioner who sees relatively few cases of pulmonary tuberculosis will be apt to find it of little use, and his time would be better spent in a complete mastery of the regular methods, which are so easily and so often slurred over, and which, properly carried out, are capable of giving him far more assistance than can the X-ray, save in exceptional instances.

For those, on the contrary, who do much diagnostic work, and thus see such cases often, or for those who devote themselves especially to diseases of the lungs, the case is different.

Here, if the doctor will provide himself with proper apparatus, and a proper dark room for its use, and will carefully examine every case which comes to him, he will soon begin to get from it information that will surprise and delight him through the light it throws upon the case, and I am very sure that he will never again give it up in his work; indeed, the experience of a friend of mine exemplifies this. Having an unsatisfactory apparatus which he used from time to time, he was satisfied that fluoroscopy was of little value in such cases, but, having had an opportunity to see what it could show with good apparatus, he adopted it in his work and took time to master it, and now uses it systematically and is a convinced believer in its great value.

I have also said that it depends upon the apparatus which the physician gets, his mastery of it, and as to whether he uses the radiograph or the fluoroscope. It need scarcely be noted that a thoroughly well-made and reliable apparatus is essential, and good apparatus for this sort of work is expensive, a satisfactory outfit costing from \$350 to \$500. Moreover, it is a *sine qua non* that the doctor have at his disposal a special dark room, or that he be able to render his consultation room absolutely dark—*satisfactory results in a room not so darkened not being possible.* In our crowded cities where office rent is high it is often difficult to have a special room or to arrange an office so that it can be absolutely darkened, but with a little trouble it can be done in any case and at no very great expense.

Again, the question of the use of the static machine or the coil is to be considered. While I personally use and prefer the former, the latter is more popular and probably the best for general use.

The static, it is true, gives a very steady light and the tubes used can be less costly and will last much longer, but the machine is notoriously hard to manage, demands a dry room, unless thoroughly understood will go on a strike in hot, damp weather, takes more place, and must be run at a high rate of speed—from 500 to 600 revolutions per minute—to give satisfactory results, which is apt to make one's neighbors complain. Hence, in the modern doctor's crowded office, the coil is probably the more satisfactory.

Finally, the feasibility of its use depends upon whether the doctor decides to use the radiograph or the fluoroscope. As is well known radiography is the recording on a photographic plate of the X-ray picture, fluoroscopy is the study of the shadow picture on a proper fluorescent screen.

Personally, I believe the former is not suitable for use by the physician himself, and consider the latter as especially adapted to a doctor's personal use. I have in a recent book[1]

[1] Klebs' Tuberculosis, pp. 269 et seq.

expressed my views fully on the subject, and cannot make myself clearer than by quoting what I have there said:

"While, however, the radiograph can at times recognize lesions undiscoverable by the fluoroscope, the difficulty is that the expert diagnostician is rarely an expert radiologist, or vice versa (or has time to become so, nor is the radiologist usually expert in the refinements of physical diagnosis).

"Moreover, the apparatus for radiography is so complex, the technique so elaborate, the time required so great, and the proper development and interpretation of the plates a matter of such special skill, that its use will necessarily remain confined to X-ray specialists to whom the patient will be sent by his physician for study and report.

"On the other hand, fluoroscopy, while in certain cases not giving as early information as radiography, gives immediate information of great value, is much less time-consuming, the apparatus and technique is much less complex and expensive, and the interpretation of the findings very much simpler, so that the physical diagnostician can easily adopt it in the routine examination of his cases without loss of time.

"Moreover, it not only gives him assistance in early diagnosis, but it will inform him of the topography of the disease and can visualize to him, as can no other procedure, the condition of the lung. . . . . While the radiograph gives such fulness of detail that it is difficult, even for an expert, to distinguish at times between normal and pathologic shadows, the picture given by the fluoroscope shows none of those misleading "normal" shadows, and is thus much easier to interpret. Correct information as to alterations in motion can only be obtained by it and except for the detection of deeply seated small foci of a ¼ inch or less in diameter, fluoroscopy is most satisfactory.

"Holzknecht says that in chest examinations radioscopy must be the method chiefly used, and F. Kraus, one of the best-known diagnosticians and clinicians, holds similar views. In short, the writer believes that the use of radiography will be confined to the X-ray specialist, and that the physician, through want of time, will most advantageously use the fluoroscope."

Diagnostic Value in Diseases of the Chest.

As a means of early diagnosis the fluoroscope, while useful, is, save in the case of bronchial gland shadows, by no means equal to an expert use of our standard physical diagnostic methods. I realize that many X-ray specialists will differ from this view, some maintaining that it is a far earlier means of diagnosis, but I am satisfied that this is chiefly due to the fact already noted, that the radiologist is rarely an expert physical diagnostician. In Germany, where several distinguished diagnosticians have used the X-ray freely, extreme claims for the early diagnostic value of the ray are not as common as in this country. We are all familiar with the ease with which the physician, unless he is specially interested in physical diagnosis, can overlook slight but significant changes yielded by inspection, percussion or auscultation. Hence, the statement that any given case was negative on physical examination and showed shadows with the X-ray is of no great value unless you know who made the physical examination. Indeed, I know of a case where a skilled radiologist with no special physical diagnostic skill made great claims of early diagnosis until he began to examine cases sent him by a notably careful physical diagnostician in a northern city, when he was surprised to find that the superiority of his method over standard methods was lost.

To quote again from myself, "the writer has not found that it can antedate rough inspiration, feeble breathing or slight vesiculo-bronchial breathing, as it must, if it is to precede physical signs, and when it is recalled what are the pathologic conditions which produce these slight changes, it seems most improbable that they should cast shadows."

If we ask, however, not whether it is a very early means of diagnosis, but whether it is a valuable means of diagnosis, I would say yes, most distinctly, and one which I would very regretfully give up in my work, and which I could not give up without greatly lessening the information I am able to gain about any given case.

Systematically used, it will be found to throw wonderful light on our work, and there are few cases, save the extremely incipient ones, in which it is not useful.

Further, as has already been noted, there is no other procedure which can give such information as to the topography of the disease, while again and again it will call to one's attention slight foci of trouble which would otherwise have been overlooked.

Before entering upon a consideration of the changes found in the different stages of tuberculosis I must refer for a moment to one or two essential points of technique which I consider indispensable if satisfactory results are to be obtained, although I will not here have time to go fully into the matter as I should like to do.

There is no diagnostic measure in which it is more essential to fully master the use of your apparatus, and the first few months of fluoroscopy will be well spent if in them one thoroughly masters the idiosyncrasies of the electrical apparatus which one has to use.

First, then, one must be sure that the tube used has a good sharp focus, else the result from it will be blurred and indistinct.

Second, I consider it *absolutely necessary* that one have a convenient means of instantaneously raising and lowering the penetration of the tube without taking your eye from the screen. Otherwise, if the tube is of high vacuum, many fine details will be flooded out, just as with the microscope when too large a diaphragm is used, while if the vacuum be too low, it will be impossible to penetrate the chest sufficiently to see anything well. It is therefore important always to use a tube of rather low vacuum with a multiple spark gap or other proper apparatus inserted in the positive side of the circuit. In this way the light can be raised and lowered at will.

Third, there must be a proper diaphragm so as to cut down or enlarge the illuminated area so that after having first examined the picture of the whole thorax, a smaller portion can be isolated and studied alone, thus bringing out details otherwise invisible, this being especially important in the comparison of the two apices.

Fourth, the fluorescent screen must be large enough to contain the shadow of the whole thorax at once, and therefore should be at least 12 by 16 inches, and better, 16 by 24 inches. The cameras usually sold with the screens on the market are worse than useless if we have a dark room, and if we have

not a dark room we might as well not try to do the work. The screen should be framed in wood, with a convenient handle in the middle of the long side as it is then easy to handle and can be held up to the chest and studied as one would study any picture.

Fifth, for the safety of the operator and to keep the room dark, the tube must be in a protective and opaque box which is lined with lead, with an opening which can be diaphragmed down, in one side, opposite the anode, and the tube must be held on a perfectly steady stand which can be easily and quickly raised and lowered during use, if the patient is to be examined erect, which is much preferable.

Sixth, the patient should be at least 2 feet from the anode, and further is better, as it lessens distortion. The transverse diameter of the patient's chest and the surface of the fluoroscope must be exactly at right angles to the course of the X-rays to avoid distortion, save during oblique radiation.

Seventh, the doctor should spend at least 5 minutes in the absolutely darkened room before starting the machine so as to render his eye sensitive, as one who comes out of the light into the X-ray room is for some time entirely unable to see properly.

Eighth, it need scarcely be noted that a complete familiarity with the normal picture is essential if pathological changes are to be recognized and understood, and that the physician should follow a systematic routine in his examination of the fluoroscopic image. I have found the following useful: 1, comparative size and shape of the two lung areas; 2, course and angle of the ribs; 3, sternal and mediastinal shadows; 4, position, size and shape of the heart; 5, motion of bases; 6, costo-diaphragmatic angle; 7, size and clearness or shading of the apices; 8, any shadows in the body of the lung.

In studying the changes found in the lung in pulmonary tuberculosis it is wise to divide them into those found in incipient cases, those in moderately advanced cases, and, lastly, those in advanced cases.

Taking up the condition in incipient cases, we find, first, no change visible, although distinct but slight physical signs are present. This is quite common in really incipient cases, although, where the radiograph is used, the percentage of such cases will be lessened. However, as Holzknecht well says, "The cases of apical tuberculosis, diagnosticated by the X-ray, are anatomically not cases of incipient tuberculosis, but old, shrunken foci only showing activity in spots. Such cases are clinically, but not anatomically, incipient tuberculosis . . . . The really anatomically incipient cases, i. e., conglomerate tubercles and catarrh, are radioscopically undeterminable."

The converse, that, after a careful and painstaking examination of the lungs, no signs will be found in a case that shows distinct shadows, is claimed by well-known authors, Williams among others, but I do not recall having seen many cases in which the findings at the apex were absolutely negative, though the X-ray showed shadows, and though deep-seated foci in the body of the lung can be found by the X-ray when undeterminable otherwise, and also though bronchial gland tuberculosis, around the roots of the lung or along the main bronchi, can thus be found before they give any physical signs.

Usually, however, the careful examiner will find shadows and changes on auscultation and percussion coexisting, and corroborating each other, and *it is this corroboration which the X-ray brings to the results of our regular examination that is one of its most valuable features.*

A very early change in incipient cases is what has been called Williams' sign, a limitation of motion of the base of the diseased lung, as compared with the good lung, which was noticed by Williams, of Boston, in 1897. While this is frequently found, I have not found it especially valuable save in corroborating the results of percussion of the bases, although it does not always agree with this latter.

When no other abnormality is found upon the screen I would not care to put too much weight on the limitation of motion of the base alone, but Williams considers it a very valuable early sign which can long antedate the appearance of auscultatory changes. Again quoting myself, I would say that "diagnostically, a slight limitation of motion of the base of one lung would raise otherwise dubious symptoms to a higher value and would make a diagnosis which would otherwise be impossible. By itself, limitation of motion is suspicious but does not justify a diagnosis."

It should here be noted that at times the limitation of motion is to be seen best in the costo-diaphragmatic angle, the angle on the affected side not opening out as fully as on the unaffected side.

Apical Shadows.

Naturally, the most valuable early sign is an apical shadow. Such shadows have unquestionable diagnostic value, and in all early cases the apices must be carefully studied, as without great care the slight shadows of incipient cases can be drowned out and overlooked.

Therefore it is important to diaphragm down the circle of light until it just includes the two apices or only one, while care must be had that the anode of the tube is on a level with the apex. In this way one apex can be compared very closely with the other and slight changes of translucence will become apparent which were invisible when the whole chest was illuminated in a large circle of light.

In order to get a complete view of the apex it should be looked at not only with the anode on a level with it but also at a higher and lower level, while, by raising and lowering the arm, the clavicle can be moved up or down, thus exposing otherwise hidden portions.

Early apical shadows are much better studied from in front than behind, though, of course, both aspects must be looked at.

Again, beginners must be careful not to be misled by the shadow sometimes cast by the crossing of the shadows of two ribs.

The French have claimed that the right apex is normally less bright than the left, but this I have not been able to

verify in my cases. The shadows in incipient cases are rarely or never dark; usually we find a grayish clouding of the apex which may or may not be accompanied by lessened size of the apex area. At times the shadow will extend down into the claviculo-sternal angle, but this is rare in early cases, though quite the rule in more advanced ones.

Again, the shadow, though usually involving the whole apex, may be limited to one portion, just as we find localized spots of apical dullness with delicate zone percussion. Occasionally the apex will be clear while there will be a small spot of shadow in the area of lung covered by the clavicle.

As I was writing this I had occasion to examine a case which I will here report briefly, since it shows well the X-ray findings in a very incipient case. The patient, Mrs. W., had a negative family history and an equally negative past history, save that in early childhood she had large chains of glands in both sides of her neck which only disappeared after an attack of mumps. The patient has always been slender but never delicate, and has lived under excellent hygienic conditions.

The present history began suddenly, with absolutely no prodromata, save pain in the left lung, and the spitting of a cupful of blood a month ago. Since that time there has been no recurrence, and at present there are no symptoms.

The X-ray examination, which, in my practice, always precedes the regular physical examination, showed a limitation of motion of the left base, especially in the costo-diaphragmatic angle, and a faint, but distinct, even shading of the left apex above the clavicle.

Inspection showed limitation of motion of the left side; also there was slight limitation of expansion on the left. Vocal fremitus was moderately increased over the left apex, front and back; vocal resonance was unchanged; the percussion note over this apex was very slightly shortened, and auscultation showed very typical rough or "granular" breathing, with a few very fine transitory dry crackles on coughing.

Here we have a case with extremely slight incipient signs in which there already existed fluoroscopic changes; more usually so light a case as this would be apt to show no changes at all by the fluoroscope.

The question arises as to what conclusions we shall draw when in a given incipient case we find shadows. Do they necessarily speak for tuberculosis by themselves? While there are no other conditions, save possibly syphilis, that we know of which will cast apical shadows, I do not believe that a shadow unaccompanied by auscultatory changes can by itself justify a diagnosis, although alone it is suspicious and calls for close watching of the case. When, however, the shadow is accompanied by signs, even if very slight ones, they would both go to corroborate each other, though, as I have already said, the shadow would be diagnostically distinctly inferior to the signs. Where one has no shadows but signs, as in very incipient cases, the absence of shadows need not cause one in the least to doubt the value of the signs as long as the physician felt he could rely upon his physical diagnostic skill.

Shadows of Enlarged Glands.

Diagnostically extremely valuable, and often preceding by some time the appearance of physical signs, are the shadows cast by enlarged bronchial glands. These are of two sorts—those around the roots of the lung and those along the main bronchi and their prolongations downward.

The latter are the more common and are seen in a large number of cases as irregular ghost-like masses of patchy shadow, often strung out like beads, and radiating downward and outward from the third rib and reaching at times nearly as low as the diaphragm, though not, of course, in early cases. In such cases they are usually seen as faint, ribbon-like, irregular bands of shadow, marked here and there by condensations. Those on the left side run so close to the border of the heart shadow as often to coalesce with it and to demand oblique illumination to bring them out clearly. They are usually better seen from in front than from behind, but even here they can stand out very clearly on the right side, running down from the fourth spine, downward and outward, more or less parallel to the inner border of the scapula. Where they are pronounced, these gland shadows are apt to send off an upward and outward branch towards the apex, as well as the downward and outward ones already spoken of, and when bilateral they make a sort of butterfly effect or a picture somewhat like the gray matter of the dorsal cord.

A case in which a very small gland shadow was revealed which otherwise would have been unrecognizable was that of a lady lately examined. She has distinct though incipient signs at the left, and to a less degree at the right apex. On the screen was seen, one inch to the left of the sternum, partly under the cartilage of the third rib, a small, very dark shadow, the size of a French bean, with the long axis vertical and surrounded by a paler gray zone the size of the end of my thumb. This was also clearly seen behind between the spine and the inner border of the scapula near its spine. This was the shadow of a bronchial gland with a calcified center. In this connection it should be noted that Koehler claims that only calcified glands can throw shadows, but while only numerous autopsies on early cases could fully settle this question, I am inclined to believe that enlarged but not calcified glands can throw shadows, and the gray peripheral portion in this case would seem to corroborate this.

A less common form of gland shadow is one projecting out on one or both sides of the sternum at the level of the second rib, and rather globular in shape, so as to suggest the shadow of an aneurism, though the distinction is not usually difficult, as unlike the latter, it does not run down into the auricular part of the heart shadow.

Of course, in incipient cases these shadows are small and light, but later get large and dense, though never so large as in the adenopathy of syphilis, where they can be very large and prominent.

The rôle that such tuberculous glands play as the source of infection not merely of the apex, but of the whole surrounding lung is well shown at times. Very recently I ex-

amined a lady who shows a distinct shadow around the roots of both lungs, the surrounding area of the lung being clear of any shading, although on auscultation the whole left lung extending outward from the root was found to be involved in an active tuberculous catarrh, lessening as it receded from the root. Again very often a slight apex shadow will be connected with an old, dense gland shadow by a band of shading.

In examining enlarged mediastinal glands oblique translumination, the ray passing from behind to one side to the point on the other side, and vice versa, is necessary for a full knowledge of the case. In this way we can see the spinal column and the heart and aorta separated by a clear strip of mediastinum, if it be free.

Before leaving the subject of the shadows in incipient cases I would note that at times in an apparently incipient case we will find old, dense areas of shadow which would indicate that the apparently incipient trouble is in reality only a reinfection from an old focus.

Findings in Moderately Advanced Cases.

In moderately advanced cases we naturally find more numerous changes, and ones which are more easily and quickly recognized. The shadows are increased in density but more especially in extent, and are found usually extending as low as the fourth rib, and, of course, generally starting at the apex. The commonest finding in moderately advanced cases in my experience, is a shadow which not only densely clouds the apex, but whose lower border runs in an oblique line from the outer portion of the clavicle, downward and inward, to the sternum at the second, third, or more rarely, the fourth rib, a similar obliquity being equally visible behind. Usually, the border of this shadow is quite distinct and sharp cut, though it may be hazy and the shadow mottled, and, here I would note that although some have denied such a distinction, I am satisfied that sharply bordered, dense or even shadows speak for a more chronic and favorable process, while lighter mottled ones with hazy outlines are found in more active and acute cases.

Shadows whose lower borders are horizontal are very much less common than those with an oblique lower border, as noted. At times the lower border of the shadow, while oblique, extends from the middle of the clavicle outward and downward, running off at the edge of the outer and upper portion of the lung area, though these, being somewhat shaded by the pectoralis, are less distinctly seen. Detached shadows in advance of the main mass of shadows are often seen here and there, and I have quite frequently found an area of shadow under the axillary fold on the left side, more or less spherical in outline with a tendency to reach inward towards the heart shadow. The shadows cast by a thickened pleura are distinguished by an even and usually light grayness, sometimes becoming, however, very dark, their lower borders ordinarily being horizontal.

Pleurisy with effusion throws a dense black shadow whose upper border is usually horizontal, though it may be curved, and change of position with motion is generally but not always present.

At times the lower border of the area of trouble will be marked off by an oblique, narrow, band-like shadow, stretching from above and outward, downward and inward, with a clear area immediately above it, suggesting a cavity, although no cavity exists, while the apex itself will be shaded. The lower limit of these oblique linear shadows at the sternum is usually the third rib, and I have regretted that I could not examine such a case at autopsy to see whether they represented a wall of fibrosis, as I have believed.

At times one finds on the back, on the right side, an intralobular pleurisy beautifully marked out by a narrow, oblique, dark line running from above and inward, downward and outward.

As is natural in moderately advanced cases, the base, if there be no effusion, is usually free of shadows.

In this stage the bronchial gland shadows already spoken of are much more pronounced and extend further downward.

Frequently the diseased lung, though not densely shaded, and often having no distinct shadows below the third rib, will be generally contracted, the outer border being distinctly nearer the midline than that of the sound lung, and that side of the chest being much smaller.

At times the lung, despite this contraction, is clear, more often it seems, while not shaded, less clear than normal, and I have wondered if it were not due to that general condensation of lung from the shrinkage that is well known to follow lessened function.

Small degrees of dislocation of the heart, the right ventricle showing unduly in the right side, or the heart being bisected by the sternum, are common in this stage as percussion has long since taught us. Dilatation or hypertrophy of the heart can also be well seen.

Where fibrosis is marked the consequent ascension of the liver is very well shown, its dome frequently rising up as high as the angle of the scapula behind, or the fourth rib in front.

Changes in Advanced Cases.

In advanced cases the chief thing looked for is naturally excavation, but there is also extensive deep shading and mottling of large areas of the lung, although even here the extreme base is usually spared. At times, however, the whole lung from apex to base is uniformly darkened usually by thickened pleura.

Where cavities are visible with the X-ray they make a very graphic and striking picture; but there seems to be no regularity in their appearance, for at times large, unmistakable cavities will be entirely invisible, and, again, small ones, not easily recognized by ordinary measures, will show up very plainly.

Cavities, to be visible, must not be too deeply seated nor surrounded by too thick a wall of condensed tissue, nor yet must the surrounding wall be too thin, and they must not be full of secretion.

When visible they show up as areas of more than normal translucence, usually rather circular or oval in outline, and surrounded by a dark area, this dark area usually merging more or less gradually into the surrounding lung tissue which itself is generally irregularly shaded. That cavities smaller than a walnut in size can be certainly recognized by the fluoroscope I do not believe.

Bronchiectatic cavities, when typical, show a more or less fusiform clear area surrounded by a narrow, dark wall, which, again, should be surrounded by normal, clear lung. I have never been certain of their recognition as I have never been able to get the only positive proof of their presence, absence of the central clear area followed by its return after free expectoration.

Dislocations of the heart already frequently visible to a small degree in moderately advanced cases, become very pronounced in advanced ones; dextrocardia on the one hand, or dislocation of the heart into the left axilla on the other, being frequently seen in fibroid cases.

In acute cases with no physical signs save hyper-resonance and numerous fine, moist and dry râles all over the lung, we find no shadows at all, as is to be expected when we recall the lesions present in this condition, which are far too small to cast any shadows.

Indeed, again and again do we find evidence of the truth of the statement by Holzknecht and others that the X-ray, whether radiograph or fluoroscope, can only recognize definite condensation of tissue (although one enthusiastic American radiologist claims to be able to recognize congestion), and since we know that appreciable condensation is not present in the earliest stages of tuberculosis, it seems to my mind satisfactorily proven that the X-ray cannot possibly recognize the very earliest changes in this disease as can auscultation.

These, briefly, are the alterations that you will find in the normal fluoroscopic picture when applied to the study of your pulmonary cases, and I trust that I have convinced you that the method has distinct value for those who are concerned with this trouble.

True, it will be troublesome to master the technique, but, in my experience, in this life only those things are easy to master which are not worth having, and he who seeks the truth must be prepared to encounter and overcome obstacles, and only he who can do this is worthy to find it.

I have tried to give you an idea of the facts to be gained by a study of the X-ray picture in pulmonary tuberculosis, and I trust that your future experience with it will satisfy you that my view of its value is correct. At the same time I hope that I have not overestimated its worth, and that I have made it clear that, as I believe, while useful as an aid to a well thought out diagnosis, it is distinctly subordinate to our regular procedures as they have been marked out for us by the master minds of our profession, by Lænnec, Avenbrugger, Piorry, Skoda, Walsh, Gerhardt, Grancher, Flint and a host of others.

Roentgen has doubtless added a valuable new weapon to our diagnostic armamentarium, but to the great Lænnec still belongs, and will always belong, the glory of having laid broad and deep the philosophical and technical foundations of the diagnostic art, and not till we have well mastered what he taught in his great work "L'Auscultation Médiate," and are capable of making an early diagnosis of Pulmonary Tuberculosis by Inspection, Palpation, Mensuration, Percussion, Auscultation and a well-taken History, should this newer method claim our time and thought.

At the same time, while I revere these past worthies, whose herculean efforts blazed the way for us to walk in, and while we value and cling to the deposit of truth handed down to us from the fathers, every broad-minded physician must beware lest he be paralyzed by the weight of authority, so strong in our profession, and must learn to bring all things intellectual to the test of his own reason, nor be slavishly bound by the old because it is the old, rather than because it is the true. His mind must be kept receptive to any new truth, or so called truth, testing its value for himself, and, if proven good, adding it to the stock of knowledge he holds as a trust for suffering humanity. Only thus can our science and art advance, building on the foundations laid by our predecessors and adding to it such truths as by patient delving and toil we may be able to unearth.

"Prove all things, hold to the good," thus alone can we find that great "Via Media" that should lead as to the truth, and whose narrow path is bounded on one side by the sterile wastes of the land of slavish acceptance of authority, where men with eyes closed cannot see the rising sun of truth, and on the other by the mirage haunted sand wastes of the desert of thoughtless worship of the new, where deluded mortals spend their time chasing the mirage of temporary fashion and novelty, mistaking it for the truth.

What else does diagnosis mean? Dia-gnosco—knowing one from another! to find the happy mean, to know the true from the false, the worthy from the worthless. Such is the aim of our art; to such a high calling are you devoting yourselves, and no pains are too severe, no efforts too great if they enable you to know the Truth.

If, then, I shall have helped you, by what I have said tonight, to decide for yourselves as to the value of this more or less new claimant for our attention, I shall be satisfied.

THE EFFECT OF DIMINISHED BLOOD SUPPLY TO THE INTESTINES UPON THE GENERAL CIRCULATION.*

By W. T. Longcope, M. D., and A. T. McClintock.

The relationship which arteriosclerosis bears to cardiac hypertrophy is a problem which for many years has interested both clinicians and pathologists; and though a considerable amount of work has been done in an endeavor to elucidate the matter, the question is by no means settled. Principally through the investigations of Hasenfeld (1) and Hirsch (2), the idea held generally at the present time is that cardiac hypertrophy does not occur in arteriosclerosis unless the thoracic or abdominal aorta or the superior mesenteric artery and cœliac axis are involved in the process. Particularly important, in these authors' opinions, is the narrowing of the superior mesenteric artery and cœliac axis. Hirsch still further suggests that since sclerosis of the splanchnic arteries is not uncommon in chronic nephritis, disease of these vessels may be an important factor in producing the cardiac hypertrophy so frequently seen in nephritis, and the cause of which is so obscure.

In spite of the fact that Marchand (3) states that he has been unable to confirm the observations of Hasenfeld and Hirsch, the idea which these authors announced has been quite widely adopted and by many to-day is accepted as a proven fact.

Since the question is really one of great importance and since there has been no experimental evidence to confirm this opinion, we decided to investigate the problem from the experimental side.

Two methods of investigation have been adopted: First, a study was made of the immediate effect upon the general blood pressure of complete occulsion of the superior mesenteric artery and cœliac axis in dogs; and second, a study was made of the effect upon the blood pressure and heart of permanent constriction of these vessels in dogs. The latter experiments will be reported at a later date. While studying the first problem so many questions came up which seemed to require elucidation that the scope of the experiments was necessarily somewhat expanded and it is the results of these investigations which will form the body of this paper.

In a previous communication (4) we have drawn attention to the rise of blood pressure which follows immediately upon constriction of the superior mesenteric artery. In this preliminary communication the technique employed is described. All the experiments were made upon dogs under ether anesthesia. The blood pressure was taken from the carotid artery by means of a mercury manometer. The vessels were carefully freed by blunt dissection of the dense plexus of nerves with which they are surrounded, and the constricting ligatures were placed directly about the clean adventitia of the artery. Pinching of the surrounding nerves by forceps and pulling upon them produced no changes in blood pressure. In these first experiments we believed that the same effect which followed occlusion of the superior mesenteric artery could not be brought about by compression of any of the other branches of the aorta, or by compression of the aorta itself below the origin of the superior mesenteric artery.

Later work has shown, however, that if the cœliac axis is occluded as it arises from the aorta precisely the same elevation of pressure is observed as when the superior mesenteric artery is compressed. In the earlier experiments not all the branches of the cœliac axis were included in the ligature. The experiments now have been repeated 45 times in 14 dogs, and always with the same result. The actual rise of blood pressure following compression of the superior mesenteric artery has varied from 8 to 22 mm. of Hg., of the cœliac axis from 8 to 22 mm. of Hg. The average rise after occlusion of the superior mesenteric artery has been 13.5 mm. of Hg. and after compression of the cœliac axis 14 mm. of Hg. When both arteries are constricted at the same time the rise is about doubled and has averaged from 18 to 40 mm. of Hg. It was found moreover that the rise in pressure is not transient, but may persist for a long time. Thus in Experiment IX blood pressure before ligature of the superior mesenteric artery was 80; immediately after the vessel was tied it rose to 92; at the end of one half hour the pressure was 94; at the end of an hour 98 mm. of Hg. After this time the pressure fell quite rapidly to 82 then 64 and when the vessel was released to 48 mm. of Hg.

It is evident therefore that mere compression of the cœliac axis and superior mesenteric artery will cause constantly a considerable rise in blood pressure which lasts over some period of time.

The question then arose as to the exact cause of this elevation in blood pressure. Two possibilities may be considered: First, that the rise is produced by a reflex from the anemic intestines; second, that it is due purely to mechanical causes and is produced by an excess of blood thrown into the general circulation after ligature of the vessels.

In support of the first hypothesis it might be argued that since it is of the greatest importance for the life of the individual that the entire intestine shall be supplied with blood, an acute anæmia of the intestine might give rise to some blood pressure raising reflex in an attempt to force blood into the splanchnic area. It is well known particularly through the experiments of Litten (5) and those of Welch (6) that sudden occlusion of the superior mesenteric artery both in men and animals gives rise to hemorrhagic infarction of the intestines which proves fatal in from 12 to 36 hours. The rise in pressure, therefore, might be compensatory, brought about by contraction of the vessels of the other viscera, and pos-

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sibly of the limbs as well, in an attempt to force blood by the obstruction or through the poor anastomotic circulation of the intestines.

If the rise of blood pressure were brought about through constriction of the vessels of the other abdominal viscera, and perhaps of the limbs, there should be a decrease in the volume of these organs during the period of elevated pressure. We have thus placed the left kidney in an oncometer and have watched the effect of compression of the superior mesenteric artery and cœliac axis upon the volume of the organ. As may readily be seen in Fig. 1 the kidney does not increase in size as it should if there were a constriction of the vessels, but on the other hand dilates, often very slightly, yet always perceptibly when the superior mesenteric artery and cœliac axis are compressed. The volume of the kidney starts to increase almost immediately upon compression of either artery, rises to a certain height and remains at this level until the artery is released when the volume falls quite rapidly to the original level. If the superior mesenteric artery is first compressed and during this time occlusion of the cœliac axis is brought about, a secondary rise takes place in the volume of the kidney corresponding exactly to the time of constriction of the cœliac axis. It could thus be shown that the increase in the volume of the kidney was directly in proportion to the amount of blood cut off from the splanchnic circulation.

An oncometer was then placed on the hind leg. After constriction of the superior mesenteric artery or cœliac axis or both vessels, there was, in this instance again, a slight but distinct increase in the volume of the leg. The effect of constriction of the cœliac axis upon the volume of the intestines was then studied. Here again we found that a slight increase in the volume of the loop of small intestine placed in the oncometer followed upon constriction of the cœliac axis. These several experiments have been repeated many times in nine dogs, always with the same result so that it is quite certain that the rise of blood pressure cannot be accounted for by a compensatory constriction of the other vessels of the body.

It is surprising, however, that since the other vessels of the body do not contract, they should not, on the other hand, dilate sufficiently to compensate for the extra amount of fluid thrown into the general circulation. This is particularly astonishing in the case of the intestines following constriction of the cœliac axis, for as has often been shown, and as we could demonstrate, it is possible for the blood vessels of the intestinal area to contain enormous quantities of fluid.

In order further to exclude reflex influences we have cut the splanchnic nerves at the level of the diaphragm and later studied the effect of constriction of the mesenteric artery upon the blood pressure. In three dogs we have noted a slight increase in blood pressure when the arteries were compressed after severance of the nerves, but the increase of blood pressure was not nearly so marked as before the splanchnic nerves were cut. Ludwig and Thiery (7) found that the rise of general blood pressure which followed compression of the abdominal aorta above or at the diaphragm was independent of nervous control, for the phenomenon took place after section of the spinal cord in the cervical region.

The results of these experiments seem to have a very definite bearing upon a somewhat similar problem investigated recently by Alwens (8). It is well known that occlusion of the renal arteries does not give rise to an elevation of blood pressure, a fact which we could confirm repeatedly. Alwens found, however, that if an even pressure equal to 95-135 mm. of Hg. was brought to bear upon one or both kidneys a very definite rise in blood pressure took place. This was evidently not due to a reflex for the rise in pressure occurred after section of the splanchnic and vagus nerves and did not appear if the blood supply to the kidney was shut off by ligature of the renal artery when the kidney was compressed. He found moreover that the rise of blood pressure following compression of one kidney was accompanied by a slight increase in the volume of the opposite kidney. He therefore concluded that the elevation of blood pressure is of a mechanical nature and is occasioned by a slight increase in the total amount of blood in the general circulation which is not perfectly compensated for by dilatation of the vessels of other organs. This lack of compensation seems, however, to hold only for the abdominal viscera. Compression of the spleen and intestines gave similar though not quite such constant results as compression of the kidney, but when the extremities were compressed, the abdominal viscera seemed capable of caring for the extra amount of blood in the circulation and there was no rise in general blood pressure.

The problem concerned is much the same as we have under consideration and it would seem very likely that there is a lack of perfect compensation on the part of the rest of the body when the blood supply is shut off from the entire splanchnic area after occlusion of the superior mesenteric artery and cœliac axis. There does seem to be some mechanism of compensation when the main arterial trunks to the limbs are compressed, for occlusion of the abdominal aorta above the bifurcation may not give rise to any elevation of pressure though we have at times obtained a rise of from 2 to 4 mm. of Hg. after this procedure. This may be due to the free anastomosis of the blood vessels supplying the limbs or it may be due to a compensatory dilation of the vessels of the viscera.

So far then as we have been able to demonstrate there is no reflex nervous action associated with the rise of blood pressure following constriction of the superior mesenteric artery and cœliac axis.

Since, therefore, the results seemed to point definitely to the mechanical rather than the reflex hypothesis, certain experiments were devised in order to obtain positive proof of the truth of this second possibility, namely, that the rise in blood pressure is caused by a sudden and persistent increase of the blood in the general circulation. The results, however, of the experiments of Cohnheim (9) and of Worm Müller (10) upon infusions of saline solution would at first seem to throw doubt upon the fact that an increase in the quantity of fluid in the circulation is capable of producing a constant or marked rise in blood pressure. Cohnheim showed that enormous

quantities of salt solution could be injected rapidly into the veins of animals without causing marked or continued rise in blood pressure. Even ligation of the splanchnic arteries did not alter essentially the result. He likewise noted that after infusion of 1000-2000 cc. of saline solution, the internal organs became permeated with fluid, though there was no edema of the subcutaneous tissues, while fluid collected in the stomach and intestines and was rapidly excreted by the kidneys.

Worm Müller, *l. c.*, stated that transfusions of blood in dogs will not increase the blood pressure to any considerable extent when the body already contains much fluid. Transfusion, however, when the body contains 20 to 30 per cent less blood than normal raised the pressure from 25 to 130 mm. of Hg. Transfusion when the body contains 25 per cent less blood than normal and continued until the body contains 30 to 50 per cent more blood than normal gives a less regular rise of pressure, but finally elevates the pressure to 120 or 175 mm. of Hg. Transfusion when the body contains 30 to 50 per cent more blood than normal produces no change in pressure.

Mall (11) on the other hand has explained the rise of pressure following constriction of the splanchnic vessels produced by stimulation of the splanchnic nerves principally upon the increase of blood thrown into the general circulation. Through a series of nicely planned experiments he was able to demonstrate that the rise in blood pressure following stimulation of the splanchnic nerves was solely dependent upon this factor. By withdrawing measured quantities of blood from the circulation at short intervals the rise of blood pressure following stimulation of the splanchnic nerves could be prevented and *vice versa* by injection of the same quantities of blood during the same intervals the blood pressure could be elevated to the same level seen after stimulation of the splanchnic nerves.

The conditions in Mall's experiments are somewhat different from what is obtained when the blood supply to the splanchnic area is cut off by simple ligation of the arteries. When the splanchnic nerves are stimulated not only the arteries of the splanchnic area contract, but as has been shown by Mall, there is also a constriction of the mesenteric and portal veins. Under these circumstances the blood is forced out of the portal vein and, moreover, the contraction of the arteries prevents the flow of blood to the entire splanchnic area. The mere compression of the superior mesenteric artery and cœliac axis, on the other hand, does not necessarily have any effect upon the finer arteries or upon the veins in the splanchnic area and besides leaves wide open whatever anastomotic circulation there may be. As it is at first difficult to reconcile the results obtained by Cohnheim with saline infusions and those observed by Mall after intravenous injections of defibrinated blood we have repeated with certain variations the main experiments.

The infusion of 0.85 per cent salt solution in eight dogs has given practically the same results as those obtained by Cohnheim. The fluid was allowed to run into the external jugular vein at the rate of from 170-200 cc. a minute under a pressure equal to one meter of water. Two hundred cubic centimeters of 0.85 per cent NaCl produced an immediate rise of pressure of 6-8 mm., which lasted only a few seconds (Fig. 3). The pressure then fell slightly below normal and gradually in the next few seconds attained the original level. Once, when at the beginning of the experiment the pressure was very low, measuring 56 mm. there was a gradual rise of 30 mm. of Hg. during the transfusion. The highest immediate rise was 24 mm. following the transfusion of 500 cc. of fluid. A thousand cubic centimeters produced practically the same result. Compression of the superior mesenteric artery during the period of transfusion gave no greater rise in pressure than before the transfusion was started. Thus in one dog the rise before transfusion was 12 mm. of Hg. during the transfusion of 500 cc. of NaCl; the rise after constriction of the superior mesenteric was 12 mm., exactly the same.

In connection with these experiments we have studied the changes which take place in the volume of the kidney, intestines and leg in the hope that by this procedure some light might be thrown upon the question as to why a more definite and persistent rise of pressure does not occur after infusion of a normal salt solution. The volume of the organs was determined by oncometric readings.

Oncometers placed on the kidney and intestines showed that almost immediately upon the entrance of the fluid into the veins the volume of these organs underwent a rapid increase. The increase in the volume of the leg was much less than with the internal organs. The increase in the size of the intestines was enormous (Fig. 3), and at autopsy after several injections of 500 cc. of salt solution, fluid, as has been noted, was found in the small intestines. Fluid had also been rapidly excreted by the kidney as was evidenced by increased distention of the bladder. It is evident then that the fluid injected into the veins very rapidly accumulates in the viscera and almost as rapidly is excreted by many of these organs. Since the intestines appeared to take up a large portion of this fluid we thought it possible that by tying the superior mesenteric artery and cœliac axis this portion of the circulation might be shunted out and more fluid would be retained in the general circulation.

It is necessary to consider here for a moment the collateral anastomosis of the intestines. As has been shown by Litten, Welch and others, quick and complete occlusion of the superior mesenteric artery leads invariably to hemorrhagic infarction of the intestines with rapid death of the animal. Though the branches of the superior mesenteric artery have anastomoses with the inferior mesenteric on the one hand and with the cœliac axis by way of the pancreatico-duodenal on the other hand, yet these connections are very inefficient for physiological purposes and it requires a very high pressure to inject by artificial means the entire region supplied by one artery through the anastomosis with the other. Litten found that it required a pressure of 300 mm. of Hg. to force coloring matter from the aorta through the anastomosis of the superior mesenteric artery into the intestines. On this account he termed these arteries physiological end arteries.

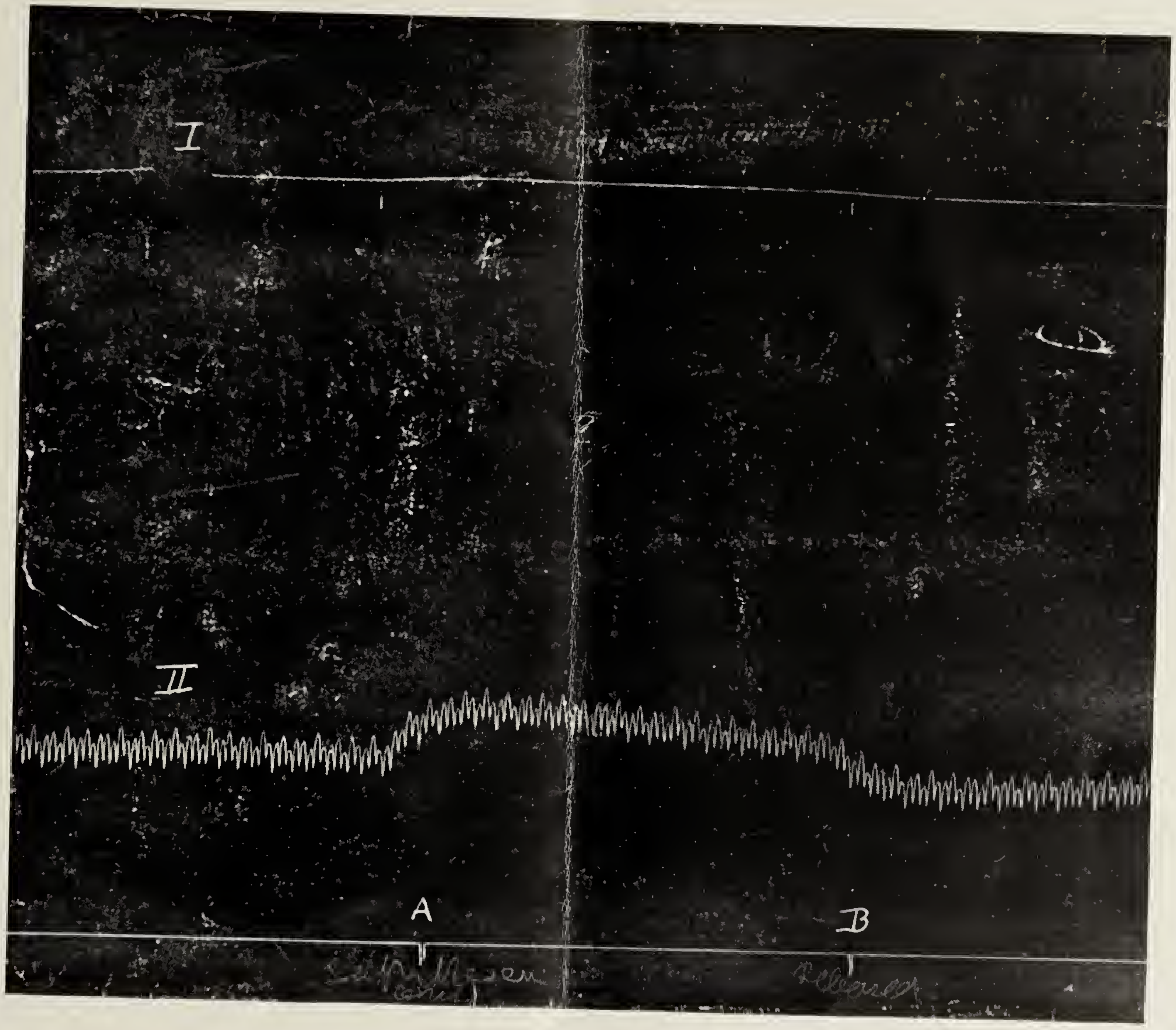

Fig. 1.—I. Volume of kidney. II. Blood-pressure from carotid artery. At *A* the superior mesenteric artery was constricted; at *B* the constriction was released.

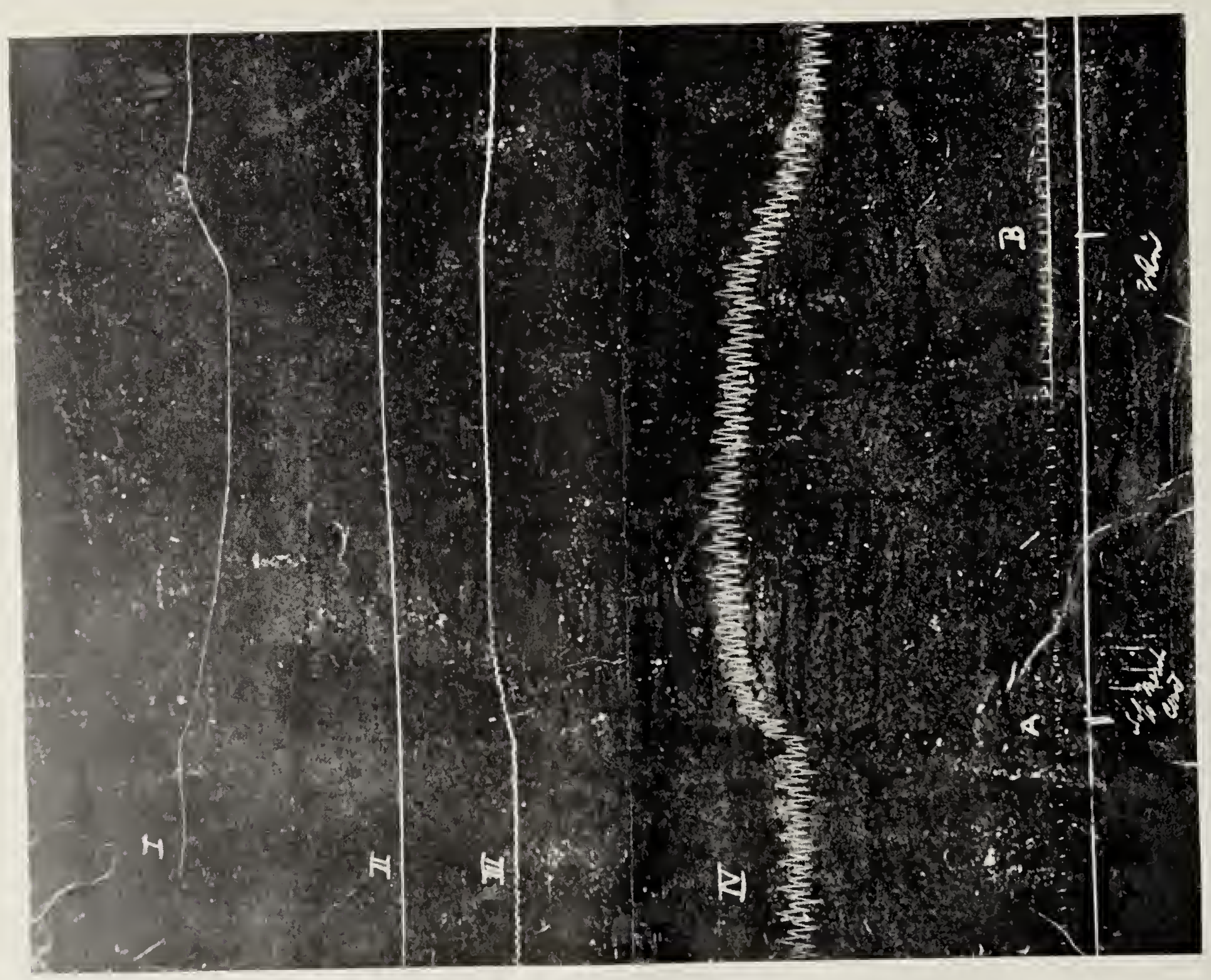

Fig. 2.—I. Volume of loop of small intestines. II. Volume of hind leg. III. Volume of kidney. IV. Blood-pressure from carotid artery.
At *A* superior mesenteric artery was constricted; at *B* the constriction was relieved.

Fig. 4.—I. Volume of loop of intestines. II. Blood-pressure from carotid artery.
At *A* portal vein is constricted; at *B* the constriction is released.

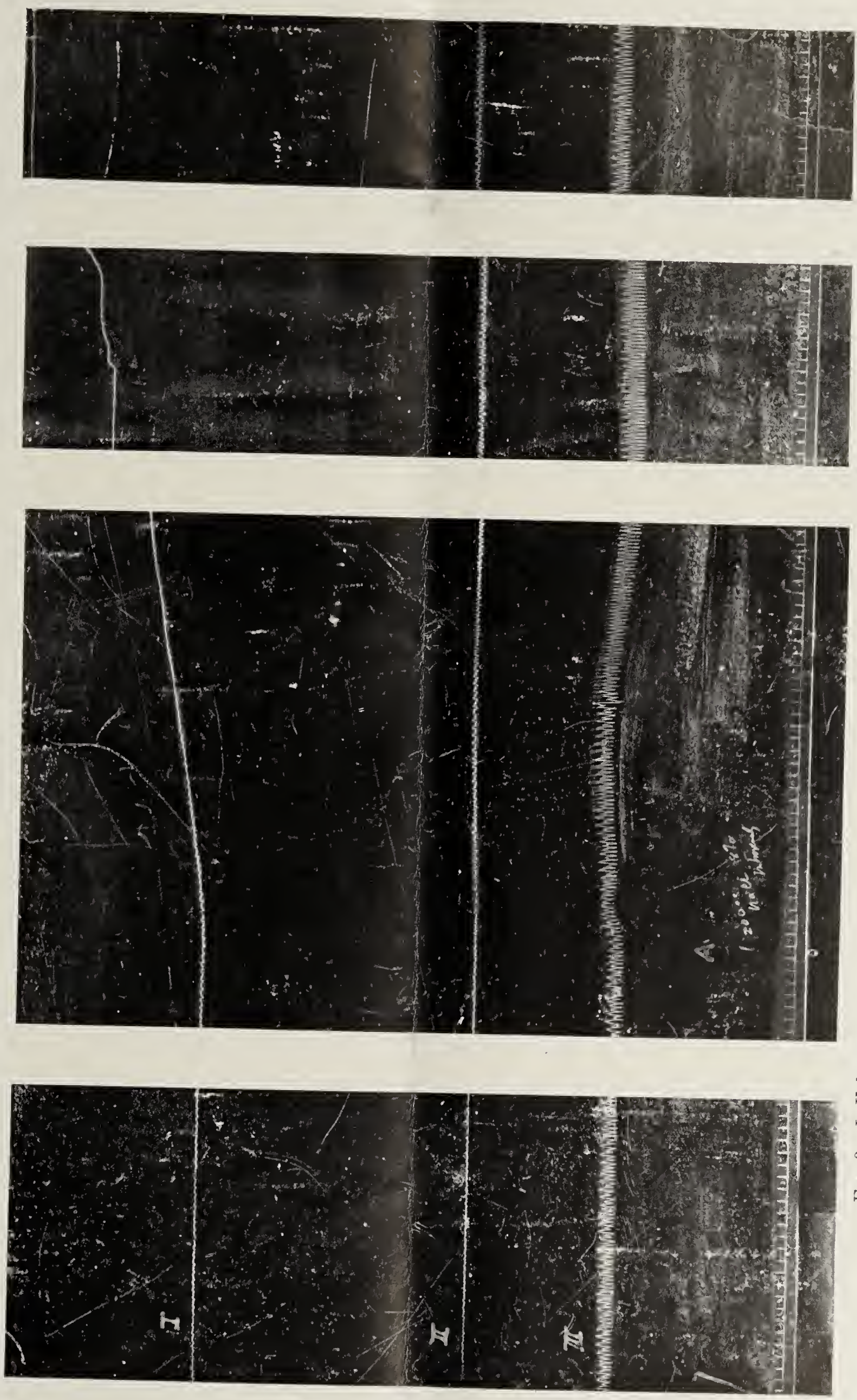

FIG. 3.—I. Volume of loop of intestines. II. Volume of kidney. III. Blood-pressure taken from carotid artery. At A 200 cc. of 0.85 per cent NaCl was infused into external jugular vein.

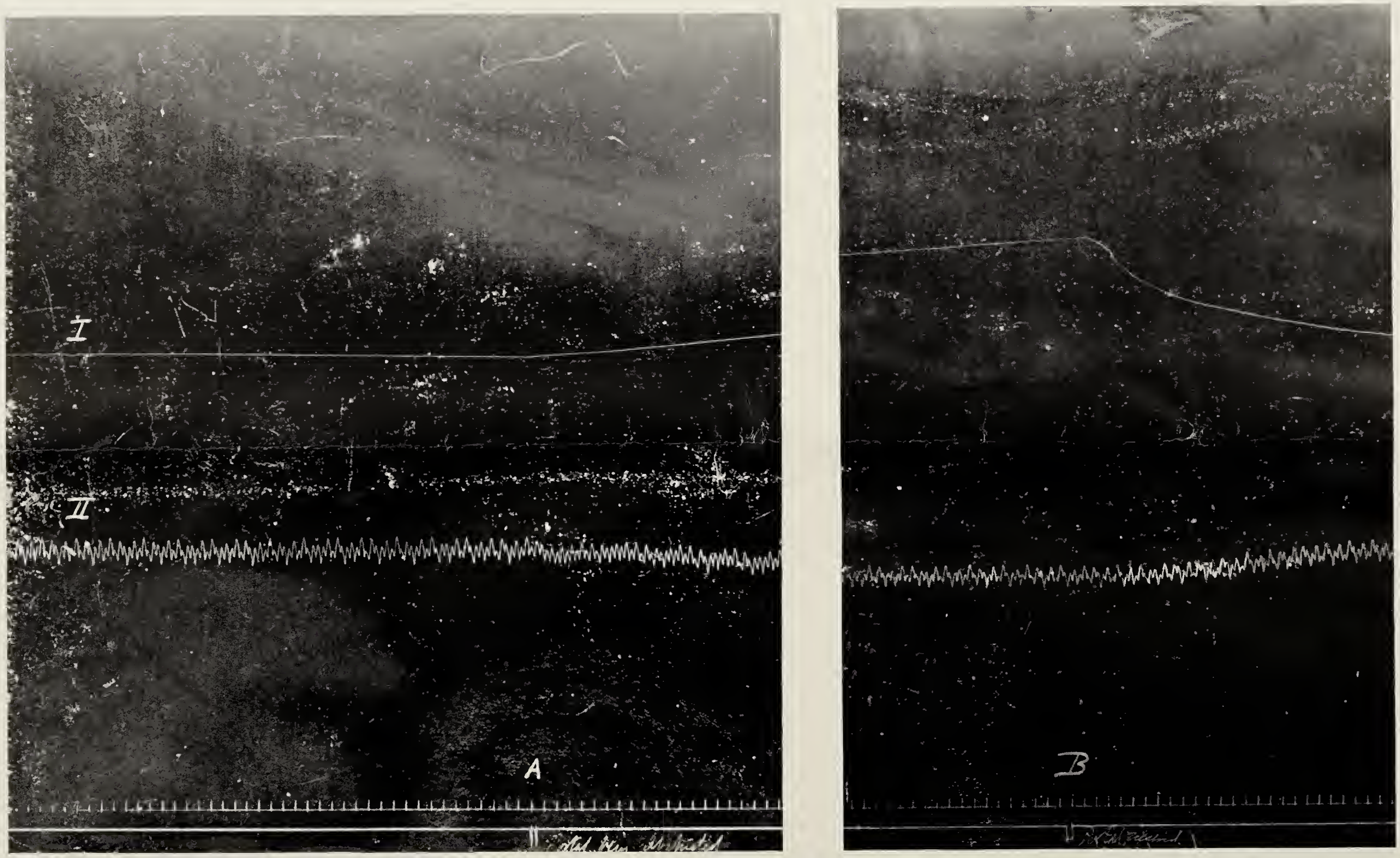

FIG. 5.—I. Volume of loop of intestines. II. Blood-pressure from carotid artery.

At the beginning of the experiment the superior mesenteric artery and cœliac axis are tied. The volume of the loop of intestines has greatly diminished and all pulsation has ceased. At *A* the portal vein is constricted. This is followed by a gradual rise in the volume of loop of intestines. 74 seconds intervenes between the two portions of the tracing. At *B* the compression of portal vein is relieved.

Infarctions of the intestines following ligation of the superior mesenteric artery are, however, hemorrhagic in character and it is evident that blood does find its way into the intestines during the formation of the infarct. This question once formed a basis for much discussion. The idea made popular by Cohnheim (12) that the blood arrived by a back flow through the veins into the infarcted area after thrombosis of the artery, was shown to be erroneous, particularly through the work of Litten and Welch, though Cohn (13) had previously stated that it was through the collateral arterial anastomosis that the blood reached the anemic area.

The following experiments show very clearly that blood does enter the intestinal area immediately upon ligation of the superior mesenteric artery and cœliac axis and that the blood reaches this region by way of the arterial anastomosis.

Under ordinary circumstances it could be shown by placing a loop of small intestine in an oncometer that pressure upon the portal vein is followed by an enormous and immediate increase in the volume of the intestines with an accompanying slight fall in blood pressure (Fig. 4). Compression of the superior mesenteric artery on the other hand, produces a marked fall in the volume of the intestines. In two instances a loop of small intestines was placed in an oncometer and the superior mesenteric artery and cœliac axis were then tied off. Following the ligature of these arteries the volume of the intestines immediately decreased. The portal vein was then compressed. Following constriction of the portal vein the volume of the intestines slowly increased until it reached the normal level; with relief of the portal vein the volume of the intestines fell rapidly, but by renewing the compression of the portal vein the volume again rose (Fig. 5).

These experiments demonstrate that immediately after the direct blood supply of the intestines, by way of the superior mesenteric artery and cœliac axis, is cut off, blood begins to flow into the anemic area by way of the arterial collateral anastomosis. Though the pressure of the blood in the superior mesenteric artery and cœliac axis is lost, still there is sufficient pressure to force the small volume of blood arriving in the anemic area into the portal vein, since there is no increase in the volume of the intestines and therefore no appreciable accumulation of blood in the intestinal area until the outflow through the portal vein is obstructed.

With the foregoing experiments as a control, .85 per cent salt solution was infused into the external jugular vein of four dogs after the superior mesenteric artery and cœliac axis had been tied. The ligature of these arteries, however, seemed to make no difference either in the rise of blood pressure or in the amount of fluid which entered the intestinal area; for after injection of 500 cc. of salt solution the rise and fall of blood pressure was almost precisely the same as in the controls where the splanchnic arteries had been left open. It is possible that the preliminary rise was somewhat longer sustained and the fall more gradual but there was no essential difference. Oncometers placed on the intestines showed the same rapid and enormous increase in volume as was noted when the arteries were open. At autopsy the small intestine and spleen were found distended and there was thin fluid in the lumen of the small bowel. When the spleen was cut, blood spurted with some force from the veins.

In order to exclude the back flow of fluid into the intestinal area through the venous channels we have tied off the portal vein together with its tributaries as well as the splanchnic arteries in two instances and have then infused salt solution. Under these circumstances the accumulation of fluid in the splanchnic region was quite as great and even greater than when all the vessels were open. After the transfusion of 1000 cc. of NaCl solution with both arteries and portal vein constricted, the intestines showed a most remarkable appearance. They were quite red and when the spleen was cut blood spurted from the mouths of the large vein with the same force as it would from an artery. In the portal vein the same thing occurred and in one of these experiments the blood spurted several inches from the mouth of the portal vein when it was cut. This may also be demonstrated by actually watching the flow of blood in the severed vessels. During the infusion of sodium chloride, after ligature of the cœliac axis and superior mesenteric artery, one of the main branches of the mesenteric artery leading to a loop of small intestines with an accompanying vein was cut. Blood flowed from the distal and proximal end of the artery, but only from the distal end of the vein. There was no pulsation in the artery. If the portal vein is allowed to remain open during this procedure the pressure, though it has never been accurately measured, does not appear to be so great.

From these experiments it may be seen that owing to the rapid accumulation of fluid in the abdominal organs after intravenous infusion of salt solution a great excess of fluid in the general circulation is obviated and as a result only a transient and slight increase in blood pressure supervenes, provided the pressure is not excessively low at the beginning of the experiment. Under ordinary circumstances after ligation of the superior mesenteric artery and cœliac axis small quantities of blood reach the intestines by way of the collateral arterial anastomosis. Infusion of salt solution after ligation of the splanchnic arteries causes, through some means, the arterial anastomosis to become more effective so that fluid accumulates as rapidly in the splanchnic areas when the vessels are ligated as when they are wide open.

It seems indeed possible that after occlusion of the superior mesenteric artery some changes in the vessels may take place which allow more ready accession of blood by way of the collateral circulation than occurs under normal circumstances. Bier, who has studied this question of collateral anastomosis so thoroughly, shows that through the lowering of the resistance in the anemic area of a limb, by reason of the dilatation of the vessels, blood flows more readily through the anastomosing arteries to the anemic part. Though this seems to be true for the limbs, he believes it holds to but a slight extent for the abdominal viscera. We have certain evidence, however, which goes to show that the same explanation may hold for the intestines. When the ligated superior mesenteric artery was released suddenly the pressure usually, but not always, fell

considerably below the original level, and in a few instances the volume of the intestines became slightly greater than it was before constriction. The fluctuations caused by the contraction of the intestines at this time, a condition to which Mall has specially called attention, makes it difficult to be sure of this point.

Since the dilatation of the vessels of the abdominal organs after infusions of salt solution is sufficient to accomodate large quantities of fluid and therefore vitiate any conclusions regarding an increase of fluid in the circulation, defibrinated dog's blood was substituted in the following experiments for salt solution. The results of these experiments which were five in number were somewhat discordant, but demonstrated that it was possible by using certain amounts of blood to raise the general blood pressure over a considerable period of time and moreover increase the blood pressure raising effect of constriction of the superior mesenteric artery and cœliac axis. The blood was allowed to flow into the jugular vein at the rate of 100 cc. in 36 seconds under a pressure of one meter of matter.

Experiment XXV.—Medium-sized dog, ether anesthesia. Superior mesenteric artery tied. Increase of blood pressure upon constriction of cœliac axis.

Before infusion	12 mm. Hg.	
After infusion of 300 cc. of defibrinated blood	28 "	24, 22, 42, 42.

Experiment XXVI.—Increase of blood pressure upon constriction of cœliac axis; of superior mesenteric.

Before infusion	10 mm. Hg.	10 mm. Hg.
After infusion of 400 cc. of blood	14 "	20, 12 mm. Hg.

Experiment XXVII.

Before infusion	10, 10 mm. Hg.	20, 24, 26 mm. Hg.
After infusion of 500 cc. of blood	10 "	14, 10, 10, 15.

Thus in the first experiments there was a distinct increase in the total rise of blood pressure following constriction of the superior mesenteric artery and cœliac axis after infusion of blood while in the third experiment when more blood was used in the infusion the rise of pressure was less after infusion than before.

The infusion of blood itself acted quite differently from salt solution. In Experiment XXIV there was a rise of pressure amounting to 24 mm. of Hg. one minute after infusion of 250 cc. of blood while after several minutes the rise amounted to 16 mm. In Experiment XXV the immediate rise after infusion of 300 cc. of blood was 20 mm. and after several minutes 10 mm. of Hg. In Experiment XXVI there was a rise of 7 mm. which lasted only about two minutes. After tying off the superior mesenteric artery and cœliac axis 500 cc. more of blood was infused and the pressure fell rapidly from 100 to 88 mm. of Hg.

In Experiment XXVII after infusion of 500 cc. of blood the pressure rose immediately 12 mm., to fall in 100 seconds to the original level. In Experiment XXVIII there was a rise of 12 mm. of Hg. following infusion of 350 cc. of blood, which lasted for nine minutes when the experiment was concluded.

Finally oncometers placed on the kidneys showed after infusions of blood very slight increase in the volume of the organ and nothing was observed to compare with the increase in the size of the kidney following infusion of equal quantities of salt solution. When the splanchnic arteries were tied before the infusion of blood was commenced, oncometers placed on the intestines showed no change in the volume of these organs up to the time when the experiments were completed.

It may, therefore, be seen from these experiments that the results obtained by infusion of salt solution and by infusion of defibrinated blood are entirely different. Following the infusion of NaCl solution there is immediate but slight and transitory elevation in the blood pressure accompanied by rapid increase in the volume of the intestines and kidney. Following infusion of blood there is moderate but definite increase in the blood pressure and if moderate amounts of blood are employed the elevation is sustained some time after the infusion has ceased. Occlusion of the superior mesenteric artery and cœliac axis has practically no influence on the changes following infusions of NaCl whereas with the blood, the pressure remains high and there is no increase in the volume of the intestines. Infusions of sodium chloride do not affect the amount of rise of blood pressure following compression of the superior mesenteric artery and cœliac axis whereas with infusions of blood the rise is often greater after the infusion than before.

The collateral anastomoses therefore act differently under the influences of NaCl solution and of blood. There are at least two possibilities which may explain the rapid accumulation of fluid in the intestinal area that takes place with infusions of salt solution after ligature of the superior mesenteric artery and cœliac axis and which does not take place with transfusions of blood. It is possible that by the addition of salt solution to the blood that the viscosity of the blood is sufficiently diminished to allow for more rapid and ready flow of fluid through the collateral anastomosis, but it is more probable that the important factor is an actual dilatation of the vessels by the direct action of the salt solution.

Schlayer and Hedinger (15) found that infusions of salt solution in normal dogs produced marked enlargement of the kidney volume with diuresis. Certain kidney poisons, notably cantharadin and uranium nitrate, injured the vessels of the kidney in such a manner that injections of sodium chloride no longer produced an increase in the kidney volume or increased excretion of urine.

In conclusion it may therefore be said that compression of the superior mesenteric artery and cœliac axis gives rise constantly to an elevation of general blood pressure which may last for at least an hour. This is not dependent upon a reflex for there is no compensatory constriction of the other vessels of the body and the rise in pressure occurs after section of the splanchnic nerves. On the contrary there is a slight compensatory dilatation of the other organs of the body which, however, is not sufficient to compensate for the increased blood

pressure. Intravenous injections of salt solution either through diminishing the viscosity of the blood or by dilating the vessels or through both means increase the efficiency of the anastomosis of the splanchnic area after ligation of the superior mesenteric artery and cœliac axis. Intravenous injections of blood do not have this effect and therefore result in a sustained elevation of blood pressure due to the increased bulk of fluid in the general circulation. The rise of blood pressure following constriction of the superior mesenteric artery and cœliac axis is due to an increased amount of blood in the general circulation. The pressure remains elevated until the excess of blood accumulates in the ramifications of the splanchnic vessels by way of the collateral anastomosis.

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THE PHYSIOLOGICAL MECHANISM OF ANAPHYLACTIC SHOCK. A PRELIMINARY COMMUNICATION.

A SUMMARY.

By Wilfred H. Manwaring, M. D.

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The development of the science of immunity has thus far been mainly in the hands of investigators, interested in the bacteriological, chemical and commercial aspects of the subject. The study of serum phenomena in their broader relationships, particularly the determination of the deeper-seated physiological reactions, of which the serum changes are conceivably but superficial indices, are parts of the subject thus far largely neglected. Yet it is probable that it is mainly through the development of this broader sero-physiology that are to come the important practical results of the future.

As an introduction to a series of such sero-physiological studies, I have chosen to investigate certain features of the physiology of anaphylaxis. The assumed importance of anaphylaxis, in the development of the theory of immunity, and the ease with which this phenomenon is studied by the simpler physiological methods, have influenced this selection.

Certain phases of anaphylactic physiology have already been studied. Thus Besredka, Gay, and others have applied sera directly to the central nervous system and nerve trunks; Biedl and Kraus, Pierce and Eisenbrey, and others have investigated certain of its vasomotor features; while Auer and Lewis have called attention to important respiratory manifestations. It is the aim of the present paper to carry the physiology of anaphylaxis, back of the phenomena studied by these investigators, to what I believe to be the primary anaphylactic mechanism, a reaction of the tissues and organs concerned in protein digestion and assimilation.

The work herein reported is part of a rather ambitious anaphylactic study, involving the use of cats, dogs, rabbits, guinea pigs, frogs, turtles, and other forms. Dogs were found most suitable for the phases of the work dealt with in this paper, and form the basis for this preliminary communication.

These dogs were sensitized by an initial subcutaneous injection of horse serum, 1 cc. to 2 cc. per kilo. of body weight, and were studied about 18 days later, under morphine-chloroform-ether anæsthesia. The anaphylactic shock was induced in these animals by an intravenous injection of dilute horse serum, the most frequently employed dose being 10 cc. of 25 per cent serum.

As an introduction to this work, numerous respiratory, blood-pressure, and plethysmographic tracings were made, nerve trunks were sectioned, electrical reactions studied, as well as reactions to therapeutic agents. This part of the work confirmed, in the main, the results of previous investigators, though my data led me to look upon the anaphylactic shock in dogs as physiologically more complex than Biedl and Kraus

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[1] Presented before the American Association of Pathologists and Bacteriologists, Washington, D. C., May 4, 1910. Summarized from the *Zeitschrift f. Immunitätsforschung*, 1910. (In press.)

It is my privilege to acknowledge my indebtedness in this work to the important suggestions of Professor Starling, and to express my thanks to his associates in the Institute of Physiology, for their cordial encouragement and criticism, that have lent so much to the pleasure of my stay in his laboratory, particularly to the many kindnesses of Associate Professor Bayliss. My thanks are also due to Professor Cushny, for his kind personal interest and suggestions. I am furthermore indebted to Dr. Martin, director of the Lister Institute of Preventive Medicine, for the hospitality of his laboratory and for numerous important criticisms, and to Mr. Twort, director of the Brown Institution, for the use of his kennels.

have assumed. This part of the work, however, was interrupted, as soon as it was discovered that all of the phenomena with which I was dealing were apparently but secondary and tertiary manifestations of a deeper-seated primary reaction.

This discovery came from attempts to locate the anaphylactic material in the body. It was shown that a cross circulation, continued for about five minutes, between an anaphylactic dog and a normal dog, usually confers immediate anaphylactic properties on the normal animal.

This proves that part, at least, of the material, formed in response to the initial serum injection, responsible for the subsequent anaphylactic condition, exists in the circulating medium. That the circulating fluid, however, is not the only store of this material, is shown by experiments, in which the blood of an anaphylactic dog is washed out and replaced by normal blood. Although such an animal is left with but negligible traces of its original circulating anaphylactin, nevertheless it may now react strongly to a serum injection.

The amount of normal blood used in these experiments was so great, and the washing-out process was extended over so long a period of time, that it is believed, not only that the circulating anaphylactin was completely washed out, but that the anaphylactin existing in the tissue spaces was also removed. It would, therefore, be logical to look upon the non-circulating anaphylactin as probably existing in combination with fixed body cells, presumably held in those cells in which it was originally manufactured.

In many cases, however, a simple cross circulation between two dogs fails to confer anaphylactic properties on the normal animal, although the sensitized animal may be shown, by a subsequent test, to be highly anaphylactic. This could be very easily accounted for by assuming the absence of a sufficient amount of circulating anaphylactin in the sensitized animal to transfer the hypersensitive condition, were it not for the fact that occasionally a dog which in itself has apparently failed to develop anaphylactic properties after the initial injection, since it gives no reaction on a subsequent serum test, is nevertheless, capable of conferring strong, immediate anaphylactic properties on a normal dog, by such simple blood transference.

These facts have led me to assume that the anaphylactin was not the only factor determining the shock. According to this assumption, the reaction would take place only when the anaphylactin is supplemented in its action by certain necessary conditions in the reacting tissues.

This view is strengthened by numerous transfusion experiments. Thus an anaphylactic dog, after recovering from the shock of one serum injection, is for some time insusceptible to a second serum dose. Nevertheless the blood of this animal, transferred to a normal dog, may confer on the latter immediately anaphylactic properties. Furthermore a dog rendered anaphylactic by transferring to it the blood of a sensitized animal, will, after reacting to one serum injection, remain insusceptible to a second serum dose, even after its blood and the waste products of the reaction have been thoroughly washed out and replaced by a fresh supply of anaphylactic blood. The reacting tissues have apparently become refractory.

To determine which tissues cooperate with the anaphylactin in producing the shock, a large amount of work was planned with isolated organs. The problem, however, proved easier of solution than anticipated. If temporary ligatures are placed about the aorta and vena cava, above the diaphragm, the upper half of the anaphylactic body will not react to a serum injection. The supra-diaphragmatic tissues and organs, therefore, are not primarily concerned in anaphylaxis. This rules out at once, the central and peripheral nervous systems and nerve endings, the cardio-vascular and pulmonary mechanisms, the connective tissue, lymphatic tissue, smooth and striped muscle as being part of the primary mechanism.

On now releasing these ligatures, allowing the serum to pass below the diaphragm, a typical shock may develop. The primary mechanism in the dog is therefore sub-diaphragmatic, and is presumably to be sought among the sub-diaphragmatic tissues not represented above the diaphragm. This confines our search at once to the abdominal viscera.

A removal of the intestines, from the pylorus to the rectum, with the attached pancreas, does not prevent the shock. A further removal of the stomach, kidneys, spleen, adrenals, ovaries, and uterus, all of which can be done in dogs without interfering with the hepatic artery, does not prevent it. We are, therefore, forced to conclude that the essential primary organ, is the only remaining abdominal viscus, the liver.

Confirmatory proof of the hepatic origin of the anaphylactic shock is, however, difficult. Attempted removal of the liver usually throws dogs into such profound surgical shock, as to render them useless for subsequent anaphylactic tests. Methods were, therefore, sought to ligate off the liver, without interfering with the circulation in other organs. As a preliminary to such attempts, it was shown that rendering dog's blood non-coagulable by defibrination, or by the use of leach-extract (hirudin), does not destroy the animal's anaphylactic properties.

If the intestine is removed, so as to eliminate the portal circulation, and if, after the injection of hirudin, a T-canula is now placed in the abdominal vena cava leading to the external jugular, the liver can be readily excluded by simple ligatures. Anaphylactic dogs, thus partially eviscerated, do not react to a serum injection. On releasing the ligatures, allowing the blood once more to pass through the liver, a shock may develop.

This operation, although it establishes the hepatic origin of the anaphylactic reaction, does not prove that the liver is the only primary organ concerned. Such proof could only come from excluding the liver from animals in which the intestine is intact. By placing an additional canula in the portal vein, carrying the portal blood also to the external jugular, this purely liver exclusion can be effected.

Of the six successful positive experiments of this nature, four animals gave no shock with the ligatures closed, but

developed reactions on their subsequent release. Two of the animals, however, gave slight shocks with the liver excluded. We are, therefore, forced to conclude that, in hirudinized animals at least, a non-hepatic shock is possible, from which we must look upon the intestine with the attached pancreas, as constituting a second, primary anaphylactic mechanism.

That the liver and intestine, however, are not the only organs primarily concerned in anaphylaxis, is shown by certain modifications of the above experiments. In the partially eviscerated animals, and in the supra-diaphragmatic half of the intact animal, in which no reaction takes place on a serum injection, it was above stated that a shock *might* develop on releasing the ligatures. It was not stated, however, that this reaction would *always* take place.

If the ligatures are kept closed but two or three minutes after the serum injection, a shock usually results. If, however, the ligatures are not released till a later period, no shock develops, although a second serum injection now, with the ligatures open, will give a typical reaction.

This shows that there is, either in the blood itself, or in the non-reacting fixed tissues, an efficient mechanism for the destruction, elimination, binding, or for otherwise rendering the injected serum anaphylactically inactive. That this anti-anaphylactic mechanism is probably not wholly situated in the blood itself, is indicated by experiments, in which a sufficient serum dose was mixed with drawn blood, the mixtures defibrinated, and reinjected about ten minutes later. On this reinjection a shock developed.

Which of the fixed body cells cooperate with the blood in producing this anti-anaphylactic effect, I have not as yet attempted to determine; but work is being planned under the hypothesis that the capillary endothelium is the principal tissue concerned in this action.

I believe I can best summarize the view of anaphylaxis necessary from the above work by defining the *acute anaphylactic reaction in dogs as an explosive auto-intoxication of hepatic and intestinal origin, which auto-intoxication is modified, inhibited and overcome, by a more or less efficient anti-anaphylactic mechanism, part, at least, of which is situated in other organs.*

As to the nature of this hypothetical auto-intoxication, whether it consists of split or conjugation products of the injected proteid, of liberated hepatic or intestinal enzymes, of an unusual amount of the normal internal secretion of these organs, or of a special internal secretion peculiar to anaphylaxis, can only be determined, after extensive histological, chemical and bio-chemical studies. The facts at present at our command do not warrant the formation of even a working hypothesis on this point.

I believe, however, that the facts above presented have a broader bearing on serum theory than their meaning in anaphylaxis. The anaphylactic material in the body clearly has its meaning, largely in terms of the functional activities of certain fixed body cells with which it cooperates. It is possible that the other substances with which we have been dealing in serology, such as the precipitins, the antitoxins, and the like, are also more complex in their reaction than usually assumed, and involve the cooperation of numerous fixed tissues. Should this be true, it would necessitate a revision of practically all our present serum concepts.

CONCERNING "COBRA-LECITHID."[1]

A SUMMARY.

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(*From the Königl. Institut f. exp. Therapie, Frankfurt a/M.; Geheimrat Paul Ehrlich, Director.*)

The most serious handicap to the development of the science of immunity has arisen from the impossibility of isolating the essential components of an immune serum in a state of sufficient purity for direct chemical study. Hence, the importance of phenomena, closely related to serum reactions, that lend themselves to direct experimental methods.

The phenomenon of this nature, that has been most extensively studied, is the phenomenon of the activation of cobra-venom by the addition of lecithin. A number of years ago, Preston Kyes, working in Ehrlich's laboratory, attempted to isolate and identify the products of this cobra-venom-lecithin interaction. Kyes first showed that, if an aqueous solution of venom is shaken with a chloroform solution of lecithin, the lecithin solution absorbs the hemolytically active venom component.

He further showed that this absorbed venom produces changes in the lecithin solution, with the formation of products insoluble in ether, so that on now diluting the solution with ether a heavy precipitate forms. Kyes showed this precipitate to be strongly hemolytic, to possess, in fact, hemolytic powers apparently equal to that of the combined hemolytic effect of all of the original components. He, therefore, conceived the precipitate to be a combination product of the hemolytically active venom component with lecithin, and proposed for it the name "cobra-lecithid." This initial precipitate he purified by an ether reprecipitation from alcohol.

Kyes's conclusion as to the nature of this precipitate is in direct accord with certain fundamental concepts of the Ehrlich school of serology. Ehrlich contends that the two essential components of an immune serum, amboceptor and comple-

[1] Presented before the American Association of Pathologists and Bacteriologists, Washington, D. C., May 4, 1910. Summarized from the *Zeitschrift für Immunitätsforschung* (1910), Bd. VI (in press).

ment, produce their prophylactic or curative effects by forming an active combination product. The proof that a mixture of venom and lecithin produces hemolysis by forming an active venom lecithid would, therefore, lend important support to Ehrlich's view.

More recently, certain investigators have expressed doubts as to the validity of Kyes's conclusion. They have pointed out that commercial lecithins usually contain comparatively large amounts of substances insoluble in ether, either in the nature of impurities or degeneration products, which substances are usually strongly hemolytic. They have also called attention to the fact that many of the artificial lecithin split products are also insoluble in ether and hemolytic, and have, therefore, felt justified in taking the stand that Kyes's product is probably nothing more than a mixture of lecithin impurities, degeneration products and split products, containing no absorbed venom, and possessing little or no serological significance.

The possibility of his precipitate being merely a venom-free lecithin derivative was, of course, recognized by Kyes in his original work. He submitted his product to Lüdecke for an ultimate chemical analysis. Lüdecke reported that its percentage composition was such that the precipitate could readily be conceived to be a lecithin molecule from which one of the oleic acid radicles had been split off.

This analysis, however, did not prove the product to be venom-free. One has but to assume the active component of cobra venom to be a substance chemically similar to lecithin, to make its presence or absence in the product indeterminate by such chemical means. Kyes was, therefore, forced to rely largely for his conclusion on bio-chemical methods.

He, therefore, performed certain immunization experiments with his precipitate with the production of antisera, the results of which were such that he was forced to conclude that his product does contain absorbed venom.

Kyes's immunization work, on which he was forced to rely so largely for this conclusion, has been repeated by von Dungern and Coca, by Sachs and other workers in Ehrlich's laboratory, and they have been unable to confirm his results. Kyes's immunizations were done during the earlier stages of his research, before his isolation and purification process was perfected, while von Dungern and Coca, Sachs and others have worked with products isolated and purified by Kyes's final method. It is probable, therefore, that this lack of agreement is due to the fact that Kyes was working with an impure, imperfectly isolated, mixed product.

Since, therefore, the immunization experiments no longer hold, the question as to the presence or absence of a venom component in Kyes's product again becomes an open one. At Geheimrat Ehrlich's request I attempted to answer this question.

One of the objections to Kyes's work was quite easily met. The contention that his product might consist largely of preformed lecithin impurities and degeneration products was shown to be without foundation, since lecithins could be very readily freed from such initial products by submitting them to a preliminary ether precipitation. After such purification lecithins yield apparently normal amounts of Kyes's product when treated by his routine technique.

That the point of view that Kyes's product might be a venom-free lecithin split product is a legitimate one, was shown by preparing artificial venom-free lecithin split products by various means, such as by the use of heat, alkalies, acids, and by long standing at room temperature. Although most of the lecithin derivatives so obtained possess properties easily differentiating them from Kyes's product, two of them are so nearly identical with Kyes's product, in all their properties, both qualitative and quantitative, as to be practically indistinguishable from it.

That lecithin could be split up into such substances, by the action of the venom lipase, was shown by experiments in which the absorbed venom was washed out of the chloroform lecithin solution, before submitting it to ether precipitation. Lecithins differ markedly in their behavior toward venom, so that a process that will yield an almost complete venom recovery from one lecithin, will give but a small venom return from a second. From the three lecithin solutions, however, from which the absorbed venom had been successfully and completely recovered, an amount of split product insoluble in ether, equal to that usually obtained in Kyes's routine technique, was isolated, the product so obtained differing in no discoverable way from Kyes's product, isolated and purified by the routine process.

This proves that, under the action of the venom lipase, lecithins may yield venom-free derivatives closely simulating Kyes's product. It does not prove, however, that Kyes's product, isolated and purified by his routine technique, is venom-free. Proof of this fact was obtained by a quantitative examination of the routine waste products.

To perform this examination, use was made of the insolubility of cobra venom in absolute alcohol. Alcohol dissolves lecithin, Kyes's product, and most of the lecithin impurities, degeneration products, and split products. It does not dissolve cobra venom. A treatment of a waste product, when necessary after evaporating it to dryness to get rid of chloroform, ether and the like, with absolute alcohol, usually yields an insoluble residue, pure venom.

These examinations, also, exemplified the marked differences between lecithins. With one lecithin the absorbed venom was recovered practically quantitatively from the first waste product, only unimportant traces being found in the subsequent by-products. With a second lecithin, the first waste product yielded but a small venom return, the main part of the absorbed venom being recoverable from the second by-product. While with a third lecithin, the absorbed venom was quite widely distributed throughout all the by-products. In all cases, however, an amount of venom, apparently equal to that originally entering into the preparation, was isolated, either from one or the other of the routine waste products, or from the combined waste products. The final product, as isolated and purified by Kyes's technique, could, therefore, not conceivably contain a venom component.

The isolation of Kyes's product gained its original import-

FIG. 1.—Three muscle cells containing areas of degeneration. Drawn with camera lucida. Oc., 3; Obj., 3; Leitz.

FIG. 2.—Showing a muscle cell with nucleus, slightly mottled area of degeneration with pink staining fibrillar strands running across it. Hæmatoxylin and eosin stain. Drawn with camera lucida. Oc., 12; Obj., 8 mm.; Zeiss.

FIG. 3.—Showing the pink mottling of the degenerated area with one small brown point at *A*. Stained with Lugol's solution and examined in water. Drawn with camera lucida. Oc., 3; Obj., 7; Leitz.

ance from the light it was assumed to throw on the nature of serum reactions. The proof that Kyes's product is a venom-lecithin compound, would have lent important support to Ehrlich's view as to the nature of amboceptor-complement action. The proof, however, that Kyes's product is only a venom-free lecithin derivative in no way weakens the Ehrlich hypothesis, since it is conceivable that an initial venom-lecithin combination actually does take place, in the Kyes technique, in accordance with Kyes's original conception, but that this initial venom-lecithin union is broken up, during the subsequent stages of the Kyes isolation and purification process.

It would, therefore, be safest, for the present at least, to regard venom-lecithin hemolysis as a process quite distinct from serum phenomena, neither confirming nor disproving existing serum theories.

A PECULIAR DEGENERATION FOUND IN HEART MUSCLE CELLS.

A PRELIMINARY REPORT.

By J. H. Hewitt, M. D.,
Demonstrator of Pathology.

(From the Pathological Laboratory of the University of Minnesota, Minneapolis, Minn.)

For the past six months we have been quite interested in a peculiar heart muscle cell degeneration observed in the routine microscopic examinations of autopsies. The finding of a second case, in a condition quite different from the first, but possessing all the distinctive characteristics of the type of degeneration, warrants, we trust, this preliminary report, that other workers along this line may confirm or refute our observations.

The degeneration in question in our cases can be readily seen on microscopic examination in heart muscle removed at autopsies. These autopsies were performed, respectively, eighteen and twenty-four hours after death. The bodies were kept in cold storage from a short time after death, until the autopsy was performed. It was seen in both instances in tissue fixed in 10 per cent formalin and in tissue fixed in Zenker's fluid. In sections stained with hematoxylin and eosin it is quite readily recognized with the low power and appears as a small round, oval, or irregular pale blue area inside of a single muscle cell (Fig. 1). No particular cells nor particular regions of the heart muscle were observed where this degeneration seemed to occur more markedly than in other portions. It occurs where there is marked proliferation of connective tissue and where there is evidence of pressure atrophy; it occurs also where there is *no* connective tissue proliferation and the cells appear slightly hypertrophied. It also occurs near the endocardium, near the pericardium, and deep in the heart muscle. In some of the cells in which this degeneration occurs the nuclei are quite prominent (Fig. 2), in others no nuclei are to be seen.

With the high power these degenerations show a slight bluish mottling, somewhat irregularly defined. Across some of them may be seen fine pink-stained lines that are continuous over into the muscle cell. These are apparently unaltered muscle fibrillæ (Fig. 2). They sometimes occupy only a portion of the cell, at other times almost the whole of the cell is filled with blue staining material, but always enough of the cell remains to show that it is a heart-muscle cell.

Besides hematoxylin and eosin, the only distinctive stain we have so far found for these degenerations is iodin in the form of Lugol's solution. These areas when so stained and examined in water appear of a terra cotta pink color, somewhat mottled and rather irregularly defined, fading away gradually at the periphery into the substance of the cell (Fig. 3). Other cells are seen in which this degeneration appears, when stained with Lugol's solution and examined in water, of a blackish brown color with a dirty pink base. On washing again in water these areas become more and more pink. In many of the pink-stained areas brownish areas may be seen. On treating sections stained with Lugol's solution with water to which a mere trace of ammonia is added the pink and brownish colors in these degenerated areas disappear; treating sections with slightly acidulated water produces no particular change.

As to the nature of this degeneration Dr. Mallory, to whom a section was kindly sent by Dr. H. E. Robertson, has expressed an opinion, that it is that of a hyaline change allied to hydropic degeneration with the presence of some mucin. However, Bismarck brown, methylene blue, and toluidin blue, which are regarded as selective stains for mucin, did not affect these areas in our cases; but this tissue had been fixed in formaldehyde and Zenker's fluid, which may have been the reason for the failure of the stain.

Sections stained in toluidin blue and thionin show abundant large-granuled cells which often are especially abundant about the blood-vessels. With toluidin blue the cell nuclei and granules are uniformly blue and resist decolorization with 96 per cent alcohol; with thionin the granules have a magenta color and the nucleus is light blue. Dr. Mallory thinks these are mast cells and the same as described by Lustgarten as the parasite of syphilis.

The case in which these degenerated areas were first met has the following anatomical diagnoses:

Gummata of brain with acute cerebral softening; tertiary luetic ulcers of legs; edema and congestion of lungs; chronic adhesive pleurisy; arterio-sclerosis; cloudy swelling of liver;

hypertrophy of prostate; acute distention of bladder and retention of urine. No bacteriological examination.

The anatomical diagnoses of the second case read as follows:

Operation wound; acute sero-fibrinous peritonitis; chronic adhesive peritonitis; multiple abscesses of liver; multiple abscesses of mesentery; chronic interstitial nephritis; edema and congestion with acute fibrinous pleurisy of right lower lobe of lung; and thrombo-phlebitis of portal vein.

Bacteriological examination showed a growth in heart's blood of a Gram-negative bacillus, unidentified (not colon). Smears from abdominal wound showed a Gram-negative bacillus and a Gram-positive coccus.

THE BACTERICIDAL POWER OF THE BLOOD SERUM OF A TYPHOID CARRIER, BEFORE AND DURING A COURSE OF ACTIVE IMMUNIZATION WITH TYPHOID VACCINES. PATIENT CEASES TO BE A CARRIER.

By F. M. Meader, M. S., M. D.,

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The object of this work was to determine, (1) the bactericidal power of the serum of a typhoid carrier for *B. typhosus;* (2) to observe the changes that occurred in the bactericidal power of the serum of a typhoid carrier, during the course of active immunization to *B. typhosus.* This report consists of the following parts:

I. Medical History of the Case.
II. Report of Observations on Case.
III. Conclusions.
IV. Technique.

I. Medical History.

Mrs. J. L., white, age 48. Native of U. S. Occupation: housework. Admitted to Women's and Children's Hospital Nov. 10, 1909. Service of Dr. John Buettner.

Complaint.—"Diarrhœa, pain in stomach, and headache."

Family History.—Unimportant.

Personal History.—Always well as a child. Went to school until 13 years of age. Never had whooping cough or scarlet fever. *When 18 years of age had typhoid fever, was sick in bed two or three weeks. About 5 years ago patient did the washing for a family in which a child had just died of typhoid fever.* When 23 years of age, patient had measles, followed by pneumonia, was in bed three weeks, subsequently was troubled with otitis media for two years.

Head.—For many years has had frequent headaches. Light error of refraction has been improperly corrected by glasses. Hearing not impaired.

Lungs.—She has had occasional cough and hæmorrhages for the last 19 years. In January, 1905, she had a cough, lost weight, and during the winter had several hæmorrhages. She was admitted to St. Joseph's Hospital August 14, 1905, complaining of pain in her head and back. Physical examination showed high pitched respiration and râles at the left apex, in the mid-axillary line; on the left side, under the 4th, 5th and 6th ribs, hyperresonance, and roughened breathing; and at both bases, behind, dull diminished breathing. August 18, tubercle bacilli, alveolar and columnar epithelium, red blood cells, and a few leucocytes were recorded as found in the sputum. On August 28, no tubercle bacilli were found, but, alveolar and columnar epithelium, red blood cells, and a few leucocytes were found. While at the hospital her temperature had an evening rise and morning fall; the highest point reached was 100° F. on two occasions, the lowest 98° F. She was discharged September 6, 1905, as improved. She had night sweats for two years subsequent to leaving St. Joseph's Hospital. Since then she has had no trouble with her lungs, and during the last two years has had several ether anæsthesias without apparent injury.

Circulatory system has apparently been normal.

Marital History.—Patient was married when 23 years of age and has had six children. They were born during her 24th, 26th, 29th, 32d, 35th, and 38th years. During her 43d year she had a miscarriage.

Genito-Urinary history is unimportant.

Gastro-Intestinal System.—Twelve years ago she began to have pain in left epigastric region, and to vomit small amounts of purplish material. The material was not frothy. Her gastric symptoms gradually became worse. At St. Joseph's there are ward notes frequently to the effect that "patient is nauseated, and vomits small amounts of blood, and complains of pain in stomach." Vomiting gave relief. After leaving St. Joseph's Hospital, September 8, 1905, her stomach symptoms did not improve. In November, 1906, she was admitted to the Women's and Children's Hospital. The stomach symptoms persisted. During the later part of January, 1907, she became nervous and anxious to return home. After discharge from the hospital she remained in bed most of the time with persistence of gastric symptoms, until she re-entered the Women's and Children's Hospital for the second time on the 16th of April, 1907, in the service of Dr. John J. Buettner, having been away about 2½ months. Symptoms of anorexia, nausea, vomiting, and pain in head and back became worse, and on August 13, 1907, Dr. R. C. MacLennan performed a posterior gastroenterostomy. A cicatricial band was found on the lesser curvature and anterior surface causing an hour-glass shape. An ulcer was also found. She was discharged September 19, 1907, with a persistence of the pain in

her stomach. About four months later (January 27, 1908) she was readmitted to the Women's and Children's Hospital for the third time complaining of pain in her side, headache and nervousness. Dr. T. H. Halsted examined her stomach with a gastroscope, but no ulcer was observed (February 27, 1908). There was spasm of the cardiac orifice, and much bloody, dark brown, material was aspirated. Subsequent gastroscopic examination was negative. She was discharged March 24, 1908. Three months later (July 5, 1908) she re-entered the Women's and Children's Hospital for the fourth time complaining of pain in her stomach. On gastroscopic examination Dr. Halsted reports that "a gray scar with a small reddened inflamed area" was observed. On July 10, 1908, Dr. Sears performed a laparotomy, but no evidence of an ulcer was seen—from external examination; a few adhesions were broken up. She recovered and was discharged August 15, 1908, apparently improved.

Intestinal Organs.—Following typhoid fever when 18 years of age, she had considerable bowel trouble, and for the last 24 years, she has had hæmorrhoids, but they have caused her little discomfort. There has been some bleeding. During the last year and a half the bowels have been irregularly, loose, and constipated. The stools have been frequently bloody, and sometimes apparently only blood was passed.

She was readmitted to the Women's and Children's Hospital for the fifth time (October 2, 1908) complaining of "tenesmus, diarrhœa, pain in rectum and nervousness." A clamp and cautery operation for hæmorrhoids was performed, and she was discharged October 13. Her symptoms returned and April 15, 1909, she was readmitted for the sixth time complaining of "pain across the front of her stomach." During the next few days she vomited some blood. It was found that placebos would relieve her pain, but she insisted upon another exploratory operation. May 1, 1909, a laparotomy was performed and incidently the spleen was observed to be enlarged, but otherwise nothing abnormal was apparent. Subsequent to this operation the vomiting decreased, but pain in the back persisted. She was discharged August 7, 1909.

After leaving the Women's and Children's Hospital, the stools became worse. A specimen of feces was sent to Dr. Wm. A. Groat at the Syracuse Medical College for examination. Following is a copy of his report:

October 30, 1909.

Liquid stool containing large amount of bloody mucus in lumps and shreds and some clear mucus. Fæcal matter in small lumps and flocculi. Odor foul and putrid.

Chemical Examination.—Bilirubin present. Occult blood test positive in liquid portion and fæcal lumps, mucus portion excluded.

Microscopical Examination.—Mucus portion contains blood corpuscles and mucus. No amœbae. Fæcal portion contains normal vegetable debris with a few striated meat fibers. No parasites or ova.

WILLIAM A. GROAT.

The stool was then given by Dr. Groat to the Bacteriological Department for examination. Typhoid bacilli were found in large numbers.* The patient entered the Women's and Children's Hospital for the seventh time November 7, 1909, complaining of "pain in stomach, frequent headaches, and loose stools."

Physical Examination.—She is a sparely nourished woman; skin and mucous membrane pale; headache is frontal; glasses apparently do not fit her; lungs negative; heart slightly dilated and pulse is irregular; no murmurs; three linear scars on abdomen, one in median line just below xiphoid process, the other two are just to the right of this scar. She complains of pain in the region of the outer scar. There are no rose spots. Liver margin is at costal border. No jaundice. Examination of spleen and kidneys is negative. Temperature is normal.

Her temperature was taken every two hours for four days. It ranged up to 99° F. once, and down to 97° F. twice.

Treatment.—Dr. Buettner tells me that as soon as it was determined that typhoid organisms were found constantly in patient's stool, she was given 15 grains of urotropin three times a day for two weeks. Then as recommended by Crowe[1] the dose was increased to 75 grains of urotropin a day. She soon began to complain of painful micturition, so that the large doses were discontinued after three or four days. After leaving the hospital (December 7, 1909) the large doses of urotropin were again attempted, but were discontinued upon the immediate return of the same symptoms. No decrease could be detected in the number of typhoid organisms eliminated in the stools.

An attempt was made to plant *B. coli* in the lower bowel in the hope that it would overgrow the typhoid organisms. The method was as follows: As she had been troubled with constipation for a time, and resorted to rectal irrigation for relief, a flask containing about a pint of a bouillon culture of *B. coli* was prepared, and she was instructed to supplement the rectal irrigation, by allowing a portion of the *B. coli* culture to flow up into the bowel. This procedure was to be repeated on four successive days. The reaction was immediate; the patient began to feel ill, had headache, and some fever, so that she could not be persuaded to continue the use of the culture. The constipation was improved for a time, but the typhoid organisms persisted in the stools. About the middle of January "Lacto-Bacillen" tablets were given to the patient, with apparently some improvement, for a time, in the action of the bowels, but no permanent relief was obtained.

During the period from December 5, 1909, to February 2, 1910, the patient was given autogenous typhoid vaccines, at intervals of one to two weeks, and the bactericidal power of her blood was examined at frequent intervals. The last injection of vaccine was on February 2, 1910, because on February 9, and subsequently, no typhoid organisms could be found in her stools.

The changes in the bactericidal power of the patient's blood are of special interest. As it is difficult to see how the

* Subsequent examination of the urine showed that it contained no typhoid organisms.

administration of urotropin or the ingestion of "Lacto-Bacillen" tablets could affect the amboceptor content of the patient's blood, the remarkable changes have been attributed to the vaccines administered.

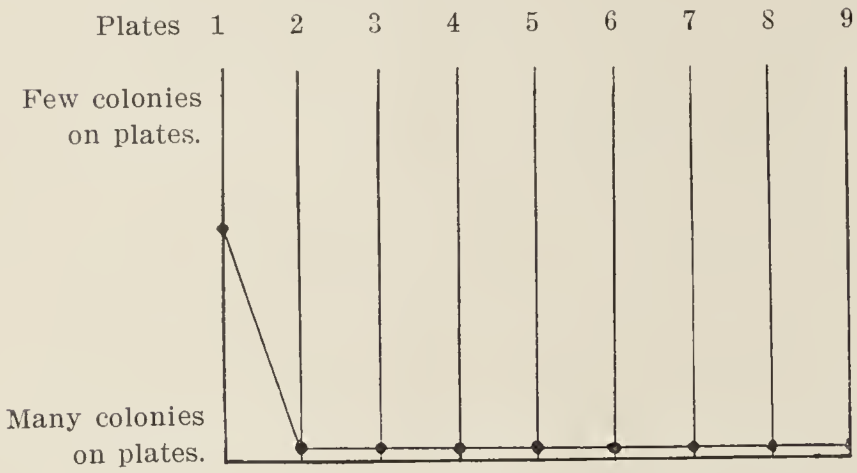
Summary.—The important points in the case are:

(1) History of typhoid fever thirty years ago.

(2) Possible reinfection five years ago.

RECORD 1.

Dec. 5, 1909.



(3) History of gastro-intestinal disturbances, diarrhœa and bloody stools for four years.

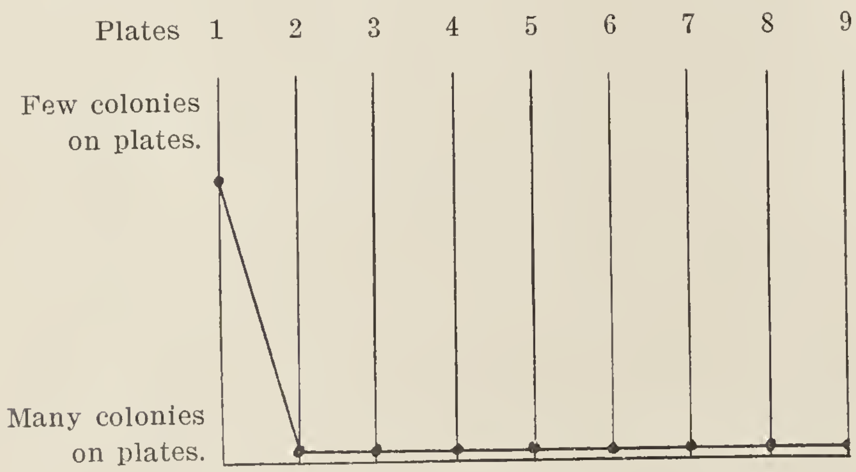
(4) Discovery of typhoid bacilli in the stools in almost pure culture.

(5) Disappearance of typhoid bacilli from stools during a course of active immunization to typhoid bacilli.

It is now proposed to report the result of the examination * of the serum of the patient, we have above mentioned, during a course of active immunization with autogenous typhoid vaccines.

RECORD 2.

Dec. 15, 1909.



II. Report of Observations on Case.

On December 5, 1909, a specimen of patient's blood was examined. The amboceptors were only numerous enough to be manifest in dilutions between 16 and 40 (Record 1).

Hahn has pointed out that the serum of normal people and those suffering from other diseases than typhoid fever, has a bacteriolytic power less than 1 to 40, but in a few cases it may be as high as 1 to 1000.

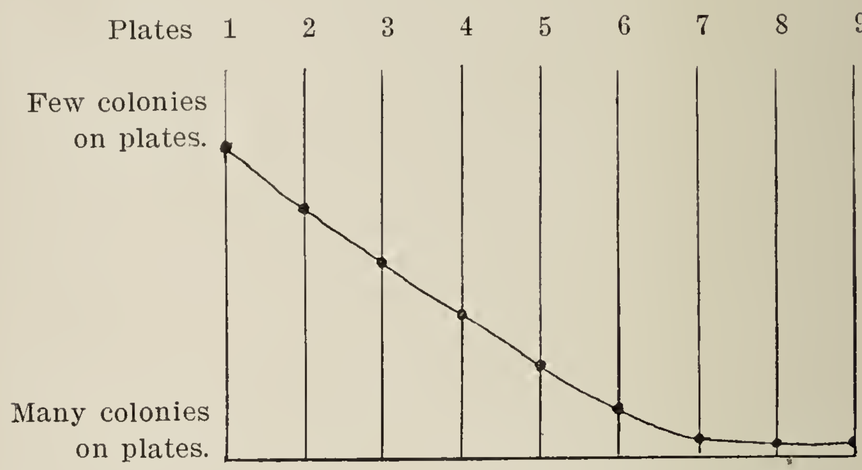
* For method used see note on Technique at end of article.

On December 15, 1909, 10 days after the last examination, a sample of blood was obtained, and the amboceptor content determined to be about as first indicated (Record 2).

So that these first two investigations, show that the bactericidal power of the blood of a typhoid carrier, as examined in vitro, may be about the same as that of a normal individual.

RECORD 3.

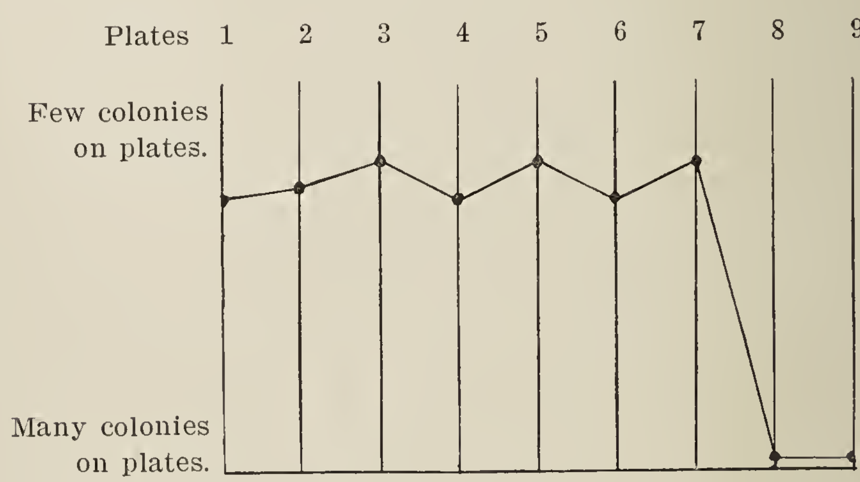
Dec. 23, 1909.



The second part of our problem concerns itself with the bactericidal power of the blood during a period of immunization. The first injection of 25 million autogenous typhoid vaccines was made December 5, 1909. No reaction in the patient was observed. Ten days later, the blood was examined again and no change was found. At this time 75 million killed bacteria were injected into the subcutaneous tissue over the biceps. There was a slight reaction next day. Patient was restless; arm was sore; and there was a red area around point of inoculation.

RECORD 4.

Jan. 7, 1910.



On December 23, 1909, 12 days after the second injection a sample of blood was obtained and the amboceptors were found markedly increased (Record 3).

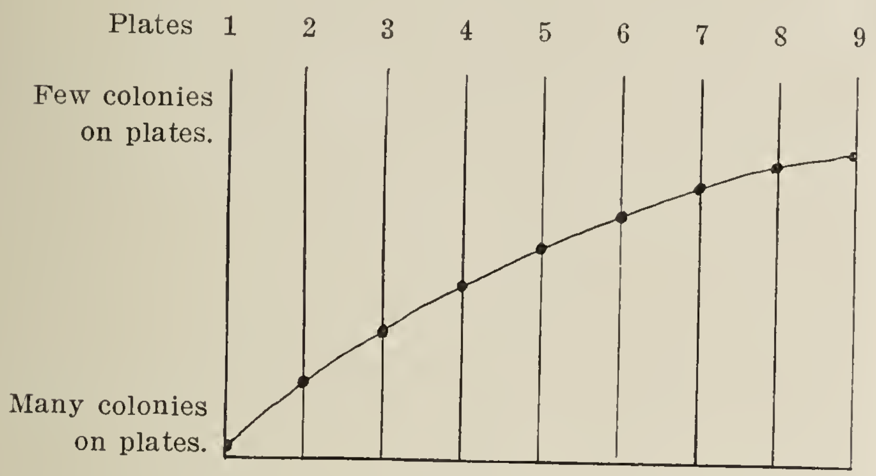
They were so numerous that a dilution of 800 to 1600 showed a marked bactericidal power. At this time, 300 million vaccine organisms were injected subcutaneously into the other arm. The reaction was more pronounced. Patient was restless; arm was painful, slight redness around point of inoculation. On January 7, 1910, 15 days later, her blood was again examined and dilutions of 1600 to 8000 showed very marked bactericidal power (Record 4).

At this time 400 million killed bacteria were injected, and on January 20, 1910, or 13 days later her blood was again examined. We obtained what, at first sight, was a disappointing result (Record 5).

Apparently the greater the amount of serum used the less was the bactericidal power, but on examination this proved to be a typical Neisser-Wechsberg phenomenon in which the

RECORD 5.

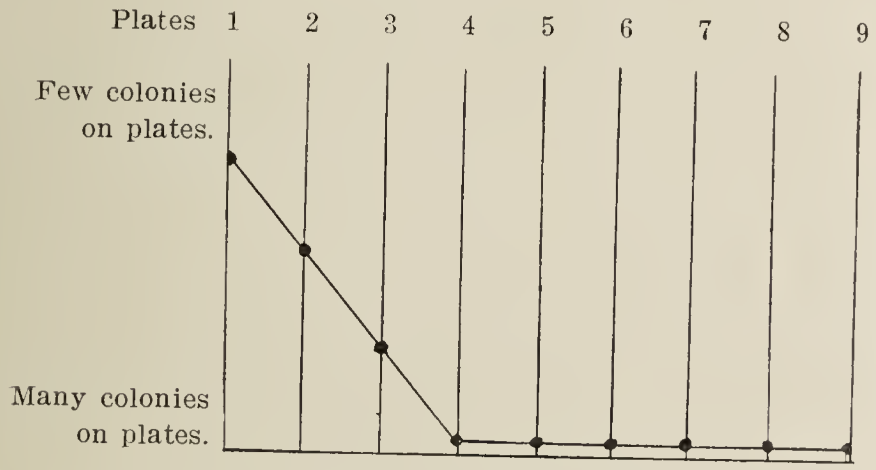
Jan. 20, 1910.



amboceptor content of the blood was so much in excess of complement that the complement was deviated from its normal course, so that the antigen-amboceptor-complement complex could rarely occur. For example, if there were five bacteria, 10 amboceptors and five complement bodies, the amboceptors would attach themselves to all the bacteria and have five left; the complement bodies would attach themselves to the amboceptors, and the chance that one complement body would attach itself to an amboceptor which was attached to a bacillus would be one-half; so that only half the bacteria

RECORD 6.

Feb. 2, 1910.



would be killed. We know that this diversion of complement was not due to anticomplement of normal serum because it had not occurred at previous examinations. That it was also not due to anticomplement formed during immunization would seem to be supported by the fact that at about this time the typhoid organisms disappeared from the stool, and further that deviation of complement did not subsequently occur. Hence, instead of being disappointed with this record, we were pleased to find the amboceptors present greatly increased, a bactericidal titer of at least 16,000.

On the day in which the last sample of blood was obtained, the patient was given 500 million killed bacteria. A small abscess formed on the arm, which was opened January 29, after which it rapidly healed.

On February 2, 1910, 13 days later, the patient's blood was examined and the bactericidal power was found much reduced (Record 6).

A dilution of only 160 to 400 would show bactericidal power. This sample was examined again and the above record was found to be correct. At the time the sample was obtained 1000 million killed bacteria were injected, and on February 9, seven days later a sample was obtained which showed a bactericidal power of only 16-40, practically the same as when immunization work began (Record 7 and 8).

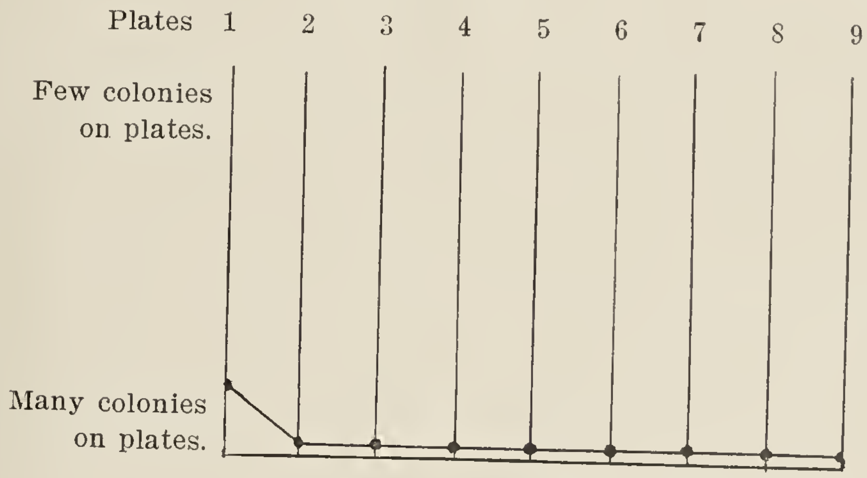
On March 7, 1910, 26 days later, patient's blood serum was examined, and the bactericidal power was found unchanged.

The general chart presents in a connected form the treatment, and results of the treatment of this case. The cross-

RECORDS 7 AND 8.

Feb. 9, 1910.

Mar. 7, 1910.



marks at the top of the chart indicate the time at which vaccines were given. The number of organisms injected are also indicated.

The heavy black line represents the change in amboceptor content of the blood.

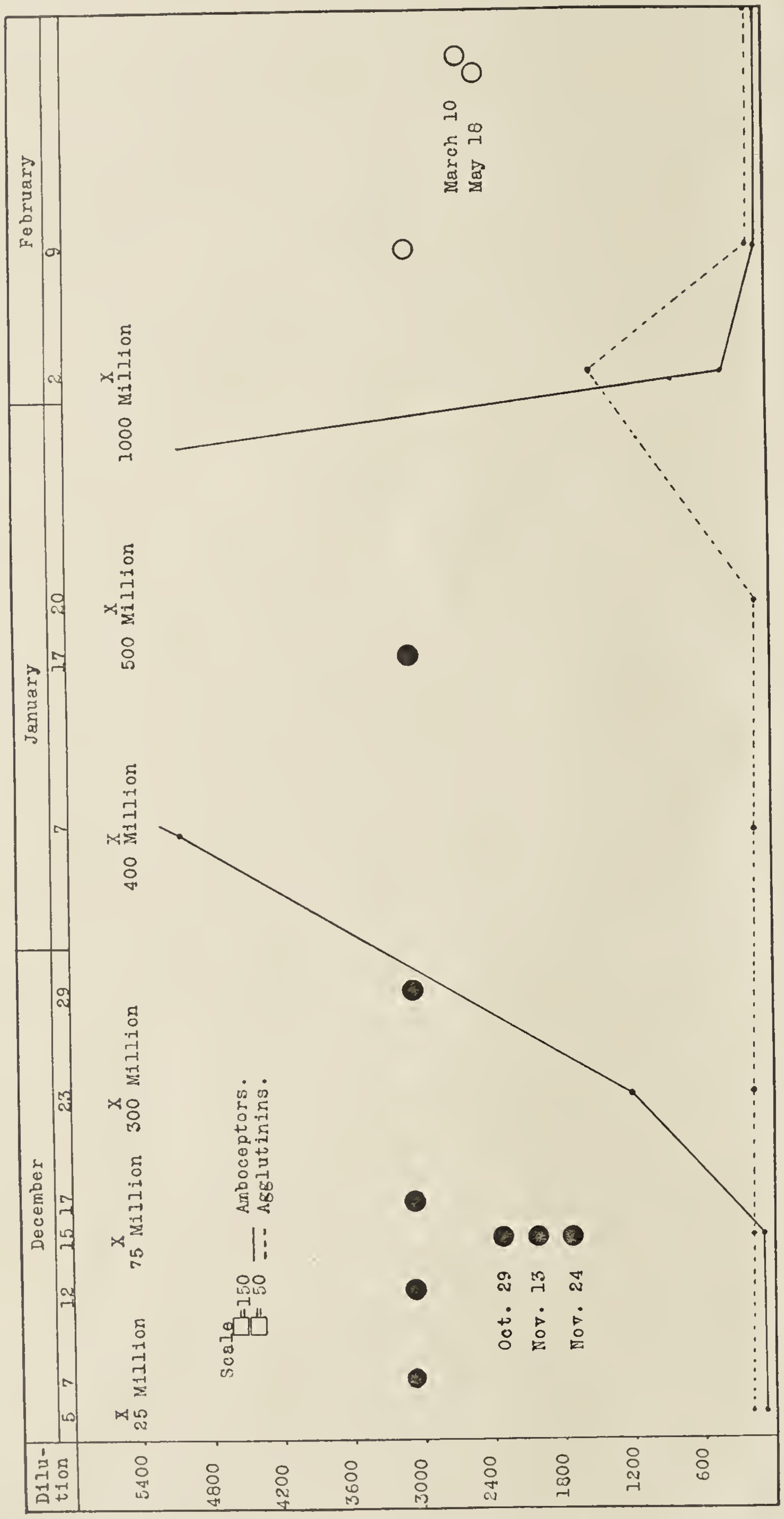
The black discs represent the stools in which the typhoid organisms were found in almost pure culture. The white discs represent the stools in which no typhoid bacilli could be found. A similar examination on March 10 and May 18 was likewise negative.

The dotted line represents the agglutinating power of the patient's serum. This power corresponds to that brought out by other observers, namely that in chronic carriers the power is low. Most of the time, this patient's serum in dilutions of 1 to 50 would agglutinate *B. typhosus* in about one hour. But, during the period of declining bactericidal power the agglutinating power becomes evident in dilutions of 1 to 500 in one hour. This increase in agglutinins rapidly came back to its usual amount when the bactericidal power had completely subsided.

When we examine the patient clinically we find that no more typhoid organisms can be found in the stool. This disappearance of typhoid organisms followed the high bacte-

ricidal titer of her serum. Again it was on January 21—just at the peak of the bactericidal power—that the patient suffered a severe nervous shock, produced by the death of her father. Whether or not this had anything to do with the decrease of bactericidal bodies I do not know, but mention it

GENERAL CHART.



merely as a point of interest. It is more probable that their decrease is the same phenomena that occurs in normal typhoid cases, that recover. This curve is very similar to those of Denison. Hence, it would seem that the vaccines stimulated the body to the elaboration of antibodies similarly to that of a normal typhoid case. (In comparing this curve with that on Chart III it will be necessary to note that the unit of the ordinate on the General Chart is 150, while on Chart III it is 10,000. The abscissa on each chart is the same.)

From a therapeutic point of view the dosage is of interest. Apparently the doses of 500 and 1000 million were not of benefit to the patient. Indeed the bactericidal power of the blood dropped at once after their administration. Whether or not this is an anaphylactic phenomena remains for future experimentation to decide. The smaller dose of 25 million apparently did not do much good. It is after the administration of 75 million up to 400 million that the greatest benefit was accomplished.*

III. Conclusions.

The results of this work may be thus briefly summarized.

1. The bactericidal power of the blood-serum of a typhoid carrier may be that of a normal person.
2. A typhoid carrier may be actively immunized to *B. typhosus* by the use of autogenous vaccines, and in so doing the bactericidal substances in the blood may be markedly increased.
3. A typhoid carrier if vaccinated so as to bring about an increase of bactericidal substances may cease to harbor the typhoid bacillus.
4. The best therapeutic dose, from an investigation of one case, seems to be 75 to 400 million.

I have to thank Dr. John Buettner for the opportunity to study this case, and for his untiring assistance in securing material for investigation. I am also under great obligation to Prof. H. S. Steensland for critical examination and timely helpful suggestion. I am also indebted to officers and trustees of the University for reference literature, laboratory facilities, and time to work upon this problem.

IV. TECHNIQUE.

(1) Preparation of Autogenous Typhoid Vaccine.

A typhoid colony is selected from a plate, made for examination of the stools. Two slant agar tubes are inoculated. After 24 hours' incubation at 37° C., 10 cc. of sterile normal salt solution is decanted into one of the culture tubes. The surface of the medium is rubbed over with a platinum wire. When the growth is apparently entirely removed, the suspension is decanted into a second tube. The growth is detached from the medium as before. The suspension is decanted into a sterile test tube containing about 3 cc. of sterile beads. The cotton plug is then replaced and after heating the upper part of the tube in a gas flame to kill any organisms that might be adherent on the inside, the tube is placed upright in a water bath at 60° C. The suspension is heated for

* Aug. 1, 1910. After the patient left the hospital last December she persistently complained of pains in the region of the gall bladder, and since this paper was prepared her symptoms became more acute, and early in July she again entered the Hospital for Women and Children. Dr. George B. Broad performed a cholecystostomy. The gall bladder was found distended and adhesions were noted about the common duct. No gall stones were present. The adhesions were removed and the gall bladder drained. A culture was taken from the normal-looking bile. No typhoid organisms could be found. The patient made an uninterrupted recovery, and now states that she "feels better than she has for years."

25 minutes (this being found to be sufficient heating to prevent further growth of the bacteria). To insure sterility, the emulsion is incubated 24 hours. Then a tube of bouillon is inoculated from the suspension. If at the end of another 24 hours, no growth appears in the bouillon tube, the suspension is examined to determine the number of bacteria per cubic centimeter.

The method of enumerating the bacteria is that used by Wright. A sterile rubber stopper is substituted for the cotton plug, and the emulsion is shaken vigorously for five minutes to break up any clumps of bacteria. The beads assist materially in this matter. A capillary pipette is prepared. A mark is placed on the glass near the top of the capillary portion of the tube. A rubber tube is attached to the large end of the pipette, and the other end of the rubber tube is placed in the observer's mouth. Draw the bacterial emulsion up to the mark above indicated. Then, after puncturing the finger of a normal person so that there is a large drop of fresh blood, draw a little air into the pipette, and then draw blood up to the mark mentioned. Remove the pipette from the drop of blood. The blood is then drawn up into the bulb, then expelled on to a clean glass slide. The mixture of blood and suspension is then drawn up into the pipette and expelled several times. Then a drop is placed upon a clean slide—near one end. The end of another slide, held at an angle of 45° with the first slide, is placed in the drop of blood-suspension-mixture and is then steadily drawn toward the long end of the first slide. This leaves an even, smooth smear, which dries rapidly in the air.

For the method of staining the smear I am indebted to Dr. Wm. A. Groat, of the Department of Chemical and Microscopical Diagnosis. A 1% solution of yellow eosin and a 1% solution of methylene blue ("für Bakteriologie") is made with methyl alcohol. The eosin solution is applied to the smear for 30 seconds; then decanted. The smear is then blotted with fine filter paper. The methylene blue solution is next applied for 45 seconds, decanted, and blotted as before. The slide is washed in a beaker of distilled water for a few seconds until the general appearance of the smear is a pink purple. Having the smear prepared, the next step is to proceed with the counting.

For this purpose, the eye piece of the microscope is removed and with a wax pencil a sharp square is drawn on the under surface of the lower lens. The eye piece is then returned to the microscope. The smear is placed under the oil immersion and a certain number of erythrocytes and bacteria are seen within the square, made by the wax pencil. The cells that are contained in the square, and those that touch two sides of the square are counted and recorded in a column. Also the number of bacteria observed in the same area is recorded in another column. Fifteen such fields are thus counted. The sum of the column of red cells is divided by the sum of the column of bacteria. Then, if 5,000,000 (the number of erythrocytes in 1 cmm. of normal blood) is divided by the quotient, and this quotient is multiplied by 1000, the product is the number of bacteria in 1 cc. of suspension. Having determined the number of bacteria in 1 cc. the amount necessary for the appropriate dose may be readily determined.

(2) Determination of Bactericidal Power of Blood-Serum.

The method of estimating amboceptors in a patient's blood is that of Neisser as modified by Denison.[2] Neisser's method has been described by several observers so that the reporting of my technique is a repetition of that which has already been recorded. My reason for reporting it is to make the record of my work complete in as great detail as possible, for only by so doing is made possible a comparison of the results on the same problem by different observers.

Materials Required.—The glass-ware necessary consists of 10 sterile Petri dishes (each having an internal diameter of about 9 cm.), 15 test tubes (10 x 1.5 cm.). These tubes are to be plugged with cotton and sterilized by dry heat. There must be two pipettes for collecting blood. These are made from a glass tube, having a 3 to 4 mm. bore. The tube is melted at one point and drawn down to capillary size. Then the tube is melted again at about 5 cm. from the previously melted area and drawn down to a capillary as above. The capillaries at each end are then broken at a point about 3 cm. from the constriction. A second tube is prepared similar to this tube except that it is twice as long. Both pipettes are sterilized by passing through a gas flame.

The next piece of glass-ware, is what Denison calls a pistol pipette. A glass tube having a bore of about 5 mm. is drawn out to a capillary. This is then broken off at a point about 4 cm. from the constriction. This makes a tube with a capillary end, of which the capillary is 4 cm. in length. Now break the tube at a point 20 cm. from the constriction. At a point 5 cm. from the large end of the tube bend the tube about 35°. The whole tube is now sterilized and the long end placed in a sterile test tube. A rubber bulb is next slipped onto the short arm of the tube. This makes a convenient instrument for measuring drops of a liquid in a precise manner.

CHART I.

Schema for Making Proper Dilutions of Bacteria, Amboceptor and Complement.

Tube number.	Drops of bouillon.	Drops of patient's serum. Amboceptor.	Drops from tube No. 11. Amboceptor 1-10.	Drops from tube No. 12. Amboceptor 1-100.	Drops from tube No. 13. Amboceptor 1-1000.	Drops from mixture of bacterial suspension and rabbit serum. Complement.	Dilution of patient's serum.
1	9	1	..	..	..	6	1-16
2	6	.	4	..	..	6	1-40
3	8	..	2	..	..	6	1-80
4	9	..	1	..	..	6	1-160
5	6	..	..	4	..	6	1-400
6	8	..	..	2	..	6	1-800
7	9	..	..	1	..	6	1-1600
8	8	..	..	..	2	6	1-8000
9	9	..	..	..	1	6	1-16000
10	10	..	..	..	..	6	Control-0
11	9	1	..	..	..	..	1-10
12	9	..	1	..	..	..	1-100
13	9	..	..	1	..	..	1-1000
14	54						

In collecting blood from the patient, it is customary to cleanse the lobe of the ear with 80% alcohol, then to puncture the ear with a sterile lance. One end of the small capillary pipette above-mentioned is applied to the point of puncture. The tube will rapidly fill with blood by capillary attraction. Next, both ends of the tube are sealed in a flame, care being taken to warm the blood as little as possible.

If it is desired to use the native complement in the experiment, the blood must be examined within two days. Otherwise, Neisser has shown that the blood may be kept in cold storage and examined at the convenience of the investigator. As is well known, amboceptors are much more viable than complement. Hence complement must be obtained fresh for each experiment. For this purpose the blood of a normal rabbit is obtained in the same manner as above described, just before it is needed. The blood from the same rabbit was used throughout the whole series of experiments.

Ten tubes, each containing 10 cc. of fresh nutrient agar-agar are required for plating purposes.

Typhoid bouillon culture is a 24-hour growth of our laboratory stock culture.

Procedure.—The 15 test tubes are numbered and placed in a rack in series. The first 9 tubes are used for holding the patient's

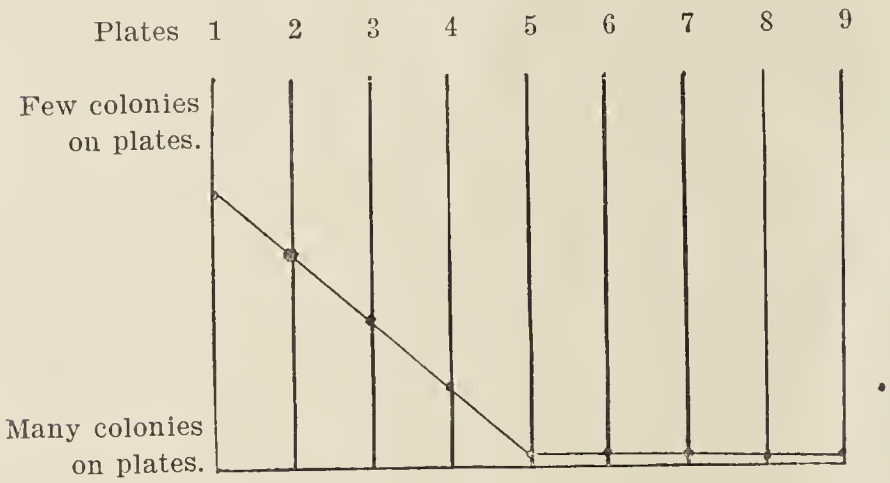
serum, complement, and bacterial suspension during incubation. The 10th tube is a control. The 11th, 12th and 13th are diluting tubes. The 14th tube is used to hold the complement and bacterial mixture. The 15th tube is for holding the pistol pipette in order to keep it sterile.

The tubes are all charged with plain bouillon in sufficient amounts to make the required dilution. See Chart I.

Having placed the required amount of bouillon in each tube, next prepare the proper dilution of the serum by placing 1 drop of the patient's serum in tube No. 1, and another drop in tube No. 11. This makes a dilution of 1 to 10 in each tube. After rinsing out the pipette with bouillon, place a drop from No. 11 in No. 12. This makes a dilution of 1 to 100. Again rinse pipette and then place a drop from No. 12 in No. 13. This makes a dilution of 1 to 1000. Again carefully rinse pipette and place the diluted serum just prepared into tubes No. 2 to No. 9, inclusive, as indicated on Chart I.

Now prepare the complement-bacterial mixture as follows: Test tube No. 14 already contains 54 drops of bouillon, add to this 6 drops of serum from the blood of a normal rabbit. Rinse pipette. Place one drop of a 24-hour bouillon culture of *B. typhosus* in about 10 cc. of bouillon. Mix thoroughly. Place 12 drops of this new typhoid bouillon preparation in tube No. 14. This tube will then contain 54 drops of bouillon, 12 drops of bacterial suspension and 6 drops of rabbit serum. Hence the dilution of the complement (rabbit serum) will be 1 to 12. Now add 6 drops of this mixture contained in tube No. 14 to each of the first 10 tubes mentioned on Chart I. The proper dilutions of patient's serum, complement and bacteria will then have been prepared. Tube No. 1 contains a dilution of patient's serum 1-16. Tube No. 2 contains a dilution of patient's serum 1-40, etc., until tube No. 9 contains a dilution of the patient's serum 1 to 16,000. The control tube contains no patient's serum. The 10 tubes are now placed in the incubator for 3 hours.

CHART II.



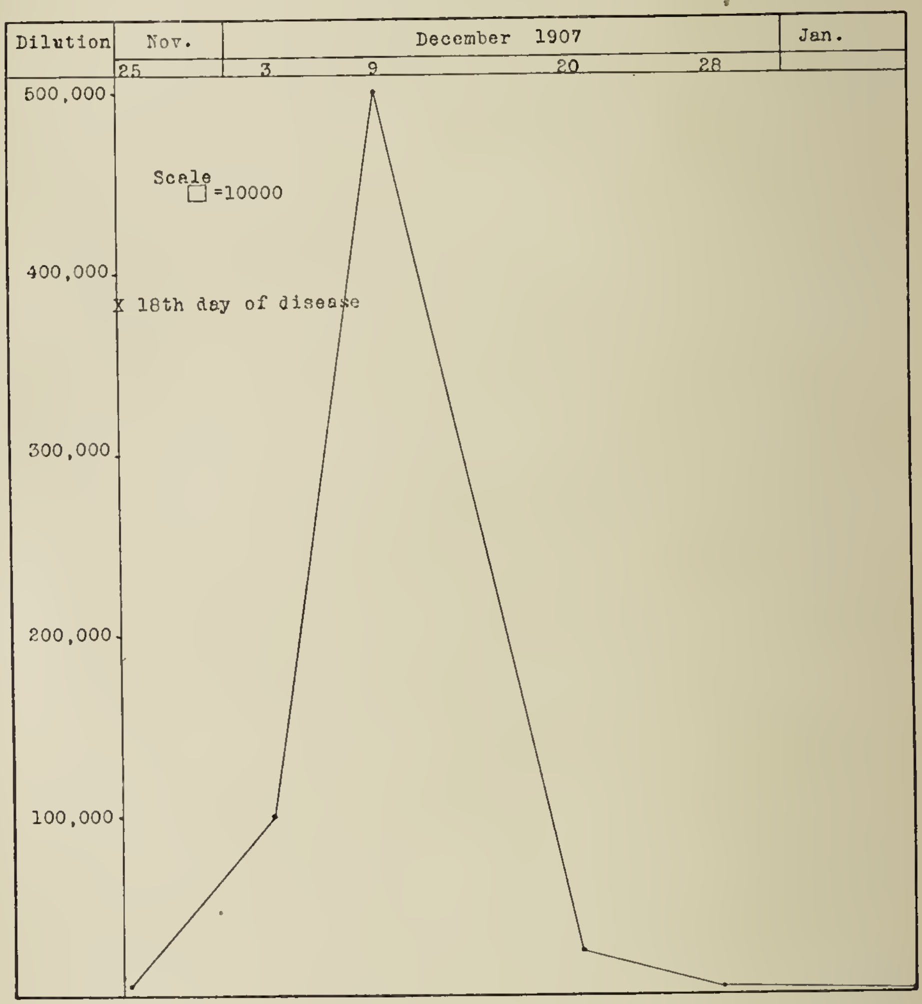
The next step is the plating. For this purpose have 10 sterile plates, and 10 test tubes each containing 10 cc. of nutrient agar-agar. Melt the agar-agar, cool, and allow to stand in the water bath at 45° C.

When the above-mentioned preparations have stood in the incubator for 3 hours, they are removed and thoroughly shaken. Then into each tube of bacterial mixture, decant a tube of melted agar-agar medium; this in turn is decanted into a Petri dish. The Petri dish is then given the number indicated by the number of the tube. When the agar-agar in all the plates has hardened sufficiently, they are inverted so that the condensation water will run down into the cover. To prevent drying and at the same time to collect the water of condensation, a convenient method is to place in the inverted lid a square of filter paper (about 5 x 5 cm.) on the middle of which is placed a drop of glycerine. The Petri dish is always kept inverted so that the medium does not become contaminated. It has the advantage over the brick covers, that it keeps the chamber moist and does not dry the medium. Incubate 18 to 24 hours at 37° C. Then arrange the plates in series according to their number. Record the relative number of colonies as estimated by comparing each plate with the control. Denison prepares a record card like the following—Chart II:

The top of the card inicates *few* colonies, the bottom of the card indicates *many* colonies on the plates. The plates are represented by vertical lines. Each plate is represented by the line of corresponding number. The record is indicated by placing a dot on the line near the top or bottom according as the number of colonies recedes or approaches the number of colonies on the control plate. The individual colonies are not counted, but are estimated by the eye. This is found to be more satisfactory and just as reliable as counting each colony. When the record for the series of plates is complete the different points on the record card are connected so that a curve is formed. The number of the line on which the curve first leaves the base line indicates the dilution of the serum at which a bactericidal action of the serum is just evident. For example, the above record of plates shows that the bactericidal properties are first evident on line No. 4. Consult Chart I and observe that No. 4 has a dilution of serum 1 to 160. Then 160 will be the bactericidal titer for the particular serum under examination.

CHART III.

Curve Showing Rapid Rise and Fall of Amboceptors in a Case of Typhoid Fever. Denison's Case 6.



If a series of observations on the serum of a patient be made during the course of a disease, the fluctuation of the bactericidal power of the serum of the patient may be indicated by a curve. This may be illustrated by such a curve taken from Denison's paper (Chart III). I have modified the curve in this way: The ordinates are made proportional to the bactericidal titer instead of indicating them by figures. This makes the form of the curve evident at once.

In reviewing this technique, it will be recalled that certain points have been rather arbitrarily indicated—for example, the number of drops of rabbit serum, and the amount of bacterial

suspension used, etc. There is a reason for using definite quantities of the various ingredients. The amounts have been determined by experiment to be the proper proportion of bacteria, amboceptor and complement in order to yield the best results and to avoid diversion of complement as much as possible. For whenever diversion of complement occurs, it will be necessary to determine whether it was due to bacterial amboceptor, anti-complement of normal serum, or the anti-complement of an immune serum (A. Lipstein [3]). Hence for the sake of precision the method as stated has been adopted.

It is stated that the serum of some normal rabbits has a bactericidal power for *B. typhosus*, and that this power varies with the season, being greater in winter than in summer. Our experiments occurred during the winter months, and the serum from a single rabbit was used. And an examination of our records indicates that the serum of the rabbit employed had no bactericidal power for *B. typhosus*.

It has been shown that the amount of complement used in these experiments is very important. If the complement be relatively too small for the amount of amboceptor present Neisser has shown that a decrease of bacteriolysis will occur due to "diversion of complement." One of my records is explained by such a supposition. Neisser points out that 5 drops of normal rabbit serum contains sufficient complement for 1 drop of serum from a patient. In my experiments the amount of patient's serum examined in each series varies from 1 drop to .001 of a drop. The amount of serum containing complement in each tube is half a drop.

In these experiments inactivation of the patient's serum was not necessary. Denison points out that a series of sera with and without inactivation were run parallel and no difference in the readings could be detected. This is probably due to the coarseness of the technique.

Neisser's method of determining amboceptors has been criticised by stating that the decrease of colonies on plates might be due to the agglutination of the bacteria into a few clumps; so that each colony instead of representing a single organism might really be due to several organisms. Neisser shows that the essential point is this, that in a series of plates in which no foreign complement is added to the fresh immune serum, the bactericidal power is manifested only in a small degree, *i. e.*, in proportion to the native complement present; whereas, in a parallel series, in which the conditions are identical except that complement is added, the bactericidal power is much increased. Now, the agglutinins in each case are the same in amount. If they were a contributing cause to the decrease in number of colonies in the last case they ought to have manifested a similar activity in the first case. But they did not produce a decrease in the number of colonies in the first case, hence we conclude that they are not at least a large factor in these experiments.

The question, as to the relative merits of the drop and pipette measurement methods, appears to be a personal matter rather than one of merit. Neisser pointed out that his method, at best, is only a rough approximation, hence it seems that the method which the observer feels he can do the best, is the one for him to use.

The question regarding the best method for determining the number of colonies on the plates has arisen. If the exact number of organisms that are put into each test tube where the bactericidal effect is brought about, could be determined, then the counting of the colonies on the plates should be the method pursued. But, since the exact number of organisms subjected to bactericidal activity is not known, the determination of the exact number of colonies on a plate is useless labor. The nearest approach to approximation is the evident relative diminution in number of colonies, which is apparent without actual counting. The result from naked-eye comparison of the plates is a more satisfactory approximation than the comparison of counted colonies—which in itself is an approximation, when large numbers are concerned. The naked-eye comparison is as good as any method at present used, and is sufficient.

In Neisser's original paper he pointed out that it was necessary to have several controls. For instance, a control to establish the sterility of the immune serum. Another to establish the sterility of the rabbit serum, and a third to determine the number of organisms put on each plate. Of course the last control is necessary, and is our No. 10. But if the immune serum is secured with aseptic precautions, and is preserved in cold storage until used, and if the rabbit serum is secured with similar precautions, these controls ought not to be necessary. Again unless the technique in collecting the serum is grossly imperfect, the number of organisms which enter by contamination would be few, and their multiplication during the three hours' incubation would hardly be sufficient to be important in modifying the results of the experiment. This point regarding the controls is a plea for a precise technique which will not be encumbered by unnecessary requirements.

It is often stated among clinicians that it is not necessary to perform such elaborate methods to determine whether or not a vaccine is beneficial. They say "watch the patient." Now, it is this kind of work that has brought about the present state of uncertainty in regard to the value of vaccines. It is easy for a skeptical person to reply that the patient would have recovered anyway without the use of vaccines. On the other hand, when a chronic case shows antibodies below a certain amount for a considerable time, and then when vaccines are given shows a rapid increase of antibodies, with recovery; when such data is available, the value of vaccines will be clearly established.

Again, the changes that are occuring among the antibodies of a patient are not always apparent in physical signs, and it cannot but be a source of encouragement to the physician as well as the patient to know that they are increasing even though their presence is not physically in evidence at the time.

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THE ASSOCIATION OF PSORIASIS WITH JAUNDICE.

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The frequent association of psoriasis with the so-called systemic diseases has been noted by different observers for a number of years. Many have attempted to trace out its etiology by studying the relation to other conditions. On account of this, the literature is filled with the histories of various constitutional affections accompanying this eruptive lesion. The present consensus of opinion seems to be that although the parasitic theory is very plausible and perhaps probable, yet one cannot fail to see other pathological conditions of a constitutional nature existing in the body in many of the cases. For instance, according to Hilbing (1), psoriasis has been observed more or less frequently with pulmonary tuberculosis, syphilis, diabetes, arthritis and in persons of a neuropathic constitution.

On the other hand, the cutaneous manifestations in icterus have been recognized for quite a long time. In 1882, Fahre (2) described at length the various eruptions which included urticaria, miliary rouge, lichen planus, furuncles, erysipelas and xanthelasma. Since then others have been observed, such as herpes zoster, eczema, dermatitis exfoliativa, measles, scarlet fever, etc. Of these the urticarial rash is probably the most common.

It is the purpose of this article to add to the above list of skin lesions complicating jaundice, another one hitherto not reported. Only the salient points in the histories are given in the following brief review of each case.

The first patient was a woman—age 45—who entered the sanitarium three years ago. Her history and physical examination were that of chronic fatigue. There was no history of any previous skin disease. A few days after admission she had a sudden attack of severe pain in the right hypochondrium radiating to the right shoulder. In a short while the stools became acholic, bile was present in the urine and a well-marked jaundice appeared over the body. There was a slight elevation of temperature and intense itching. After a period of twelve to fifteen days, the icterus gradually faded away, but with this disappearance there developed a generalized diffuse eruption characterized by small patches of scaly maculo-papular elevations typical of psoriasis. After three weeks, all the lesions disappeared and the skin assumed its natural condition. (Unfortunately other details cannot be given on account of an incomplete history).

The second case entered the sanitarium last winter, male, age 27, medical number 4570. His chief complaint was jaundice and breaking out on the skin. The past history was entirely negative. The present illness began four weeks ago with diarrhœa, nausea and a general feeling of malaise. The temperature was 100° F. At this time there was a faint icteroid tint, becoming very pronounced in four days. Two days later a few scaly papules appeared on the wrists, which in a short period became general. On admission the skin and conjunctivæ were decidedly yellow. Scattered over the trunk, arms and legs—both on the flexor and extensor surfaces—there was a diffuse maculo-papular eruption. It was non-inflammatory, in places confluent, forming large well-defined patches. The various reddish areas were covered by silvery scales which on removing left bleeding points. There was considerable itching. The lesion was most marked on the chest, the skin in the axillæ being almost entirely covered by the confluent eruption. The genitalia were also involved, but to a less degree. The urine showed the presence of bile, but otherwise was negative. The stools were clay-colored. The patient was discharged four weeks later with no jaundice and with a very marked improvement in the psoriasis. A report from him six weeks later states that the eruption still persists, but to a less degree.

In these two cases we have a very interesting and apparently similar condition. In view of the fact that the underlying cause of psoriasis is not definitely established, the appearance of this generalized eruption with a systemic toxæmia may throw some light on its etiological basis. Neither case had ever had psoriasis, but both developed a similarly distributed eruption with the jaundice. Quoting from Stelwagon, "psoriasis lesions are noted to form sometimes along the line or at the points of mechanical irritation." It is conceivable that the possible scratching incident to the jaundice may have caused sufficient irritation to bring about the cutaneous manifestations, but the wide area involved seems to preclude such an idea.

The not infrequent occurrence of psoriasis with glycosuria may be explained in a similar manner, as in both conditions there is a deposit of foreign elements in the skin. However, until the true etiology of this malady is definitely established, the relation of the above diseases cannot be accurately determined.

I am indebted to Dr. C. P. Emerson for his permission to report these cases.

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THE JOHNS HOPKINS HOSPITAL BULLETIN.

The Hospital Bulletin contains details of hospital and dispensary practice, abstracts of papers read, and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly.

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PEMPHIGOID ERUPTIONS IN TYPHOID FEVER.

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The cutaneous manifestations in typhoid fever have become in recent years the subject of a very close analysis. The great variety of these lesions make a most fascinating study from a dermatological point of view. In the long list of complications some more or less rare or anomalous eruptions are found. Among these pemphigus may be mentioned as a distinctly uncommon one.

It is the object of this paper to report briefly two cases of typhoid fever showing a pemphigoid eruption during the course of the disease. In looking over the literature, one is impressed by the extreme rarity of this condition and the paucity of the writings bearing upon this subject. In not a single treatise upon typhoid fever is pemphigus included among the eruptive complications. In a very excellent thesis, Monnier (1) discusses pemphigoid eruptions associated with the so-called eruptive fevers, but typhoid is not considered among them. Cabiran (2) in 1879, and Da Costa (3) in 1899, made an exhaustive study of the cutaneous phenomena in typhoid fever, each describing fully the common as well as the uncommon eruptions. In neither of these reviews, however, is the interesting condition taken up which forms the subject matter of this article. The only well-authenticated case recorded in the Surgeon-General's Catalog was reported by de Santi (4) in 1880. A synopsis of the history is as follows:

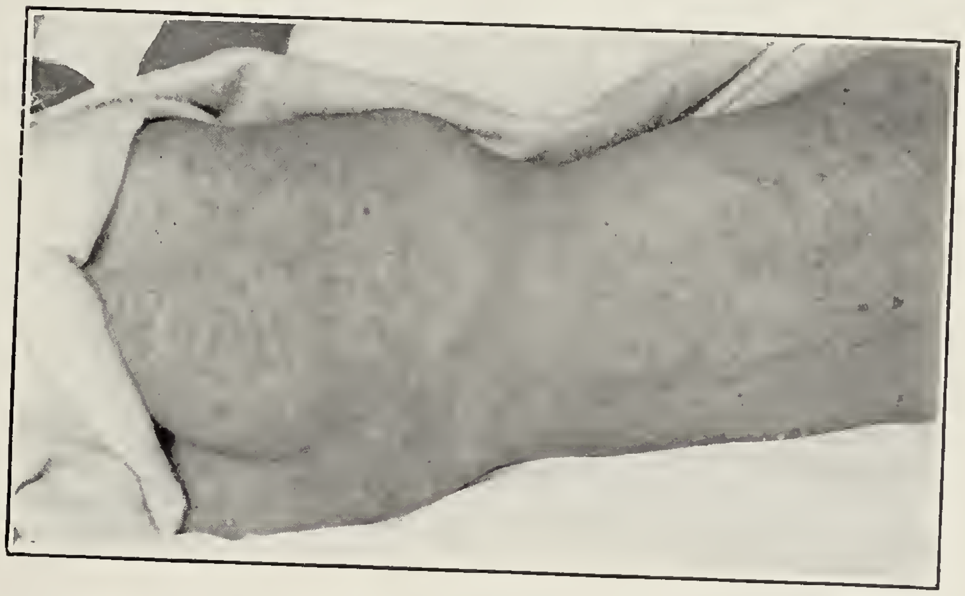
A very robust plethoric male adult entered the hospital apparently on the fourth day of his illness. There was a high grade of toxæmia manifested by hyperpyrexia, stupor, persistent headache and diarrhœa with some distention. On the seventh day, a profuse crop of rose spots appeared over the abdomen. On the twelfth day, the general condition became decidedly worse and over the buttocks, flanks, and thighs there was for the first time a pemphigoid eruption characterized by about twenty bullæ varying in diameter from 4 to 10 mm. They overlaid normal skin and were composed of a simple pellicle of epidermis, some being filled with a clear fluid, while others contained a purulent material. This eruption existed for four days or until his death. At autopsy there were found in addition to the typhoid lesions a capillary bronchitis and a parenchymatous nephritis.

In the 2191 cases of typhoid fever treated at the Johns Hopkins Hospital, up to September, 1909, there have been two showing this pemphigoid eruption. The first one (5) is a particularly interesting case and will be referred to at the conclusion of this report. The history and physical examination are as follows:

Lewis R., Hospital No. 20,507, white, age 39, admitted September 4, 1897. The significant points in his past history are an attack of typhoid fever four years ago lasting for three months and malaria for several seasons. He was a laborer on a Maryland farm and exposed daily to the sun. He entered the hospital complaining of dumb chills, fever, diarrhœa and sore throat.

His present illness dated back for about seven weeks. During the early part of this period a numb-like feeling, general malaise and heat of the sun prevented him from working more than one-half of the time. One week ago his condition became worse. His diarrhœa which began at the onset now caused him to have seven or eight stools in the twenty-four hours. There was no associated abdominal pain nor blood in the stools. Two days ago his throat became sore and his sister says he talks thicker than usual and is becoming deaf. No nose bleed nor headache. Appetite has been very poor.

Physical examination.—Patient is a poorly nourished man with sandy hair. His sun-burned face, open mouth, sallow complexion give to him a rather apathetic expression. Eyes are dull, pupils react normally. Lips are rather blue, mucous membranes pale. Tongue coated white, bright red and inflamed and slightly fissured around the dorsum. Posterior pharynx is dull white and is crossed by several large blood-vessels giving it the appearance of an old chronic catarrh. Neck is reddened by the sun with well-marked dermatographia. Over the backs of both hands are two



large patches covered by scabs, probably an infected dermatitis, as he says they came from scratching. This condition has been present for five weeks. Liver dulness normal, Spleen just palpable. Urine and blood are negative. The Widal positive. The examination was otherwise normal.

On the sixth day after admission there appeared on the dorsum of the right hand a subcutaneous collection of blood elevating the skin about 0.5 cm. and measuring about 1.5 cm. in diameter. The contents of this bleb consisted of a yellowish, thick material, showing microscopically many pus cells, a few red blood cells and a few chained cocci (?). The patient stated that the dry crusts were the remains of other bullæ similar to the one described. He continued to be dull and heavy, running very irregular fever and a pulse around 100. Two or three "suspicious" spots appeared in the flank. After a relapse of three weeks, his condition improved gradually and he was discharged well seven weeks after admission. At this time only a few crusts remained on the hands.

The second case gave the following history:

Mary H., Hospital No. 65,106, white, age 17, admitted August 24, 1908, on what was apparently the sixth day of the disease. She complained of headache and soreness in the abdomen. This patient was extremely toxic, developing a marked grade of delir-

ium and a cholecystitis shortly after her admission. On the twenty-second day there was a very extensive furunculosis involving the neck, arms, the buttocks and back. Scattered among these infected areas and especially over the fore-arms was a primary skin lesion of a bullous type accompanied by a very slight superficial inflammatory reaction. Each bleb was round and elevated, varying in size from 1.5 mm. to 1 cm. in diameter. They were discreet and well defined bearing no relation to the hair follicles. In some of these vesicles, the fluid was clear, while in others it was distinctly purulent. There was no associated pain nor hyperæsthesia. (See photograph.) After a prolonged convalescence, the patient recovered. At the time of discharge practically all of the vesicles had disappeared.

The question which naturally arises is what possible relation may this complication bear towards the general course and outcome of the disease? On account of the limited number of cases which have been reported, only a tentative deduction may be made as to the prognosis. All three cases had at least one other complication, and in two of them, the bullous eruption appeared during the height of the disease and was accompanied by other signs of severe toxæmia. It is interesting to note that in the two extremely ill patients, the distribution was more or less general, while in the least toxic, only the dorsa of the hands were involved. In analyzing the history and physical findings of this latter case, No. 20,507, one cannot refrain from surmising whether we are dealing with a type of pellagra rather than a complication of typhoid. Although the diagnosis was made by Dr. Osler in 1897, the previous history of typhoid, the present illness, physical examination and the general course of the disease present a more typical picture of the former than the latter malady. Unfortunately, the patient has been lost sight of and it is not known whether other symptoms developed later or not.

Pemphigus itself is classed among the uncommon skin lesions, and judging from this review it is an extremely rare occurrence with typhoid fever. However its infrequency will undoubtedly become less marked as the cases become more closely studied. In conclusion one may make the assertion, although based upon the observations of only three cases, that the occurrence of a pemphigoid eruption in the course of typhoid fever is an omen of rather grave significance.

I am indebted to Dr. L. F. Barker for permission to report these cases.

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ACROMEGALY AND GOITRE. REPORT OF A CASE.

By W. E. Grove, M. D.,

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Acromegaly has been scientifically known since 1886 when Pierre Marie described two cases of his own and others in the literature. It is a comparatively rare disease, only 262 cases with 77 autopsies being on record in 1902 (Woods Hutchison). In addition to the constant finding of lesions in the pituitary body, 12 out of the 24 cases in which the thyroid was examined showed a hypertrophy of that gland. In a condition as rare as this one, any case which seems to throw some light on the subject should be recorded, and it is the association with the acromegaly of several other interesting features that prompts me to present this history. I consider it unnecessary to give a bibliography with the report of a single instance and refer those interested to a complete bibliography on the subject in Dock's excellent article on acromegaly.[1]

The case is that of a white woman, aged 47, general number 3520, who was admitted to this sanitarium complaining of exhaustion and a swelling of the neck.

In the *family history* of the patient the only important features are that the father died of pulmonary tuberculosis and the mother of gall stones.

In the *past history* of the patient the fact that she never menstruated is very important. The rest of her past life is not significant. Fifteen years ago the patient had a severe attack of influenza from which she recovered very slowly. An external strabismus of the right eye has existed since early childhood. The patient has always been more or less constipated.

Present Illness.—Two years ago the patient first noticed a swelling of the neck. This did not trouble her much until about one year ago when she commenced to have difficulty with breathing. During the last year the tumor has grown progressively larger and at present the patient wears a No. 15 collar. During the last three or four years the patient has noticed that her hands and feet were growing larger, the size of her gloves increasing from 6 to 8 during this time and the size of her shoes from 6 to 7½. She has not noticed any difference in the size or shape of the head, although her husband states that he has noticed a difference in the shape of the patient's nose, it being broader at the base. The patient does not think she has increased in height during recent years. She has not noticed any progressive nervousness and does not

[1] Dock—Acromegaly—Osler's Modern Medicine.

complain of headache. She does complain of considerable exhaustion and of chronic constipation.

Physical Examination.—The appearance of this patient is absolutely typical and the diagnosis was made on inspection. The patient is a woman of very large, angular frame, 5 feet 11 inches in height and weighing 167 pounds. The head is very large, square and heavy in appearance. The patient gives a distinct impression of gawkiness. The nose is large and heavy at its extremity. The lower jaw is large, square and rather heavy and the lips are prominent. The cheek bones are not particularly prominent. There is present a considerable external strabismus of the right eye. No evidence of hemianopsia can be found on rough testing. The examination of the left eye with the perimeter shows a slight limitation of the peripheral field of vision (Fig. 1). The peripheral field of the right eye could not be obtained because of the external strabismus, although the eye is not completely

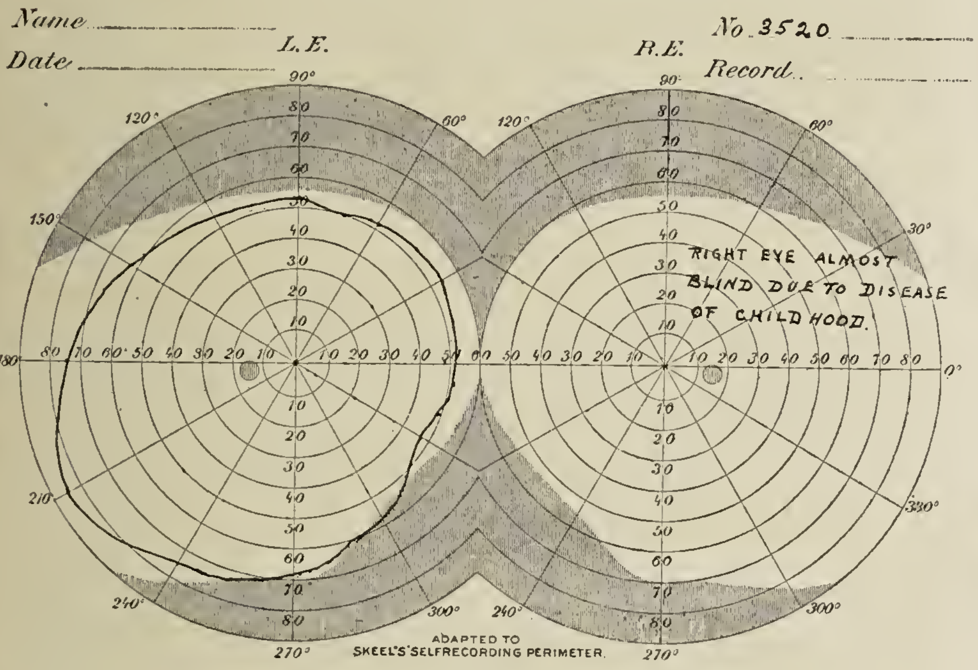

Fig. 1.—Perimeter chart of the left eye.

blind. A decided spacing of the teeth in both upper and lower jaw is noticed.

The skin, on the whole, is decidedly sallow and very dry. The mucous membranes are quite pale. The tongue, thick and with indented edges, is covered with a thin moist grayish coat. The throat is negative and the tonsils cannot be made out.

There is no enlargement of the lymph glands of the neck. There is present a very positive enlargement of the thyroid gland, which seems to affect the whole gland, but especially the right lobe. The isthmus also is enlarged and has a tense elastic feeling. Both lobes are smooth with the exception of a nodule at the upper pole of the right lobe. No bruit or pulsation can be made out over the gland.

The pulse is 76 to the minute, regular in force and rhythm, of normal volume and tension. The vessel wall is not sclerosed. The systolic blood pressure averages 138 mm. Hg.

The lungs were entirely negative.

Heart.—The point of maximum impulse is easily located on inspection in the 5th interspace 8.5 cm. to the left of the midsternal line and about 2.5 cm. medial to the left mammilary line. Deep cardiac dulness extends 11 cm. to the left in the fifth, and 5 cm. to the right in the third interspace. At the aortic area there is a soft systolic blow accompanying the first sound; the second aortic is relatively more accentuated than the second pulmonic. At the apex there is a faint systolic blow, heard also slightly beyond the point of maximum impulse. Otherwise the heart sounds are clear.

The abdomen is negative. The liver reaches just to the costal margin in the right mamillary line and its edge is distinctly palpable as it descends on inspiration. The kidneys and spleen are not palpable.

The right hand is out of all proportion with the right forearm, measuring 22.5 cm. in circumference not including the thumb. The fingers are almost uniform in circumference and very thick. The relative proportion of the hand is good. The feet also are considerably increased in size. The toes are all enlarged and slightly clubbed. The nails are small in comparison to the size of both the fingers and toes.

The urinary findings are absolutely negative. The patient's blood showed 77 per cent hæmoglobin, 4,472,000 red blood corpuscles, 5280 white blood corpuscles, and a practically normal differential count with the exception of a slight relative increase in the large mononuclear and eosinophilic elements.

Polymorphonuclear neutrophiles	65%
Small mononuclear cells	20%
Large mononuclear cells	10%
Polymorphonuclear eosinophiles	5%
Total	100%

In order to study the general metabolism of the patient she was placed upon Folin's standard diet for five days, the daily amount being as follows:

Whole milk	500 cc.
Cream (18—2.2% fat)	300 cc.
Eggs (white and yolk)	450 gm.
Horlick's malted milk	200 gm.
Sugar	20 gm.
Sodium chloride	6 gm.
Water q. s. ad	2000 cc.
Extra drinking water daily	900 cc.

My analyses of this food showed that it contained daily about 16.9 gm. nitrogen and 11.6 gm. sodium chloride. The total urine was examined each day for chlorides as NaCl, urea, ammonia, and total nitrogen. The feces were saved for five days and at the end of that time were carefully evaporated with alcohol and examined for their total nitrogen content. The patient's weight at the beginning and at the end of the five days was the same, 167 pounds. The following table will explain itself and gives the results of these analyses:

Date 1909	Amt. of Urine in cc.	Specific gravity	Total N in gm.	Urea in gm.	Ammonia in gm.	Chlorides as NaCl in gm.	Total N. in feces in gm.
Aug. 20	1850	1014	10.471	21,271	0.377	12.950	
Aug. 21	2230	1014	12.800	25.199		12.934	
Aug. 22	1870	1015	13.015	26.941	0.338	10.098	
Aug. 23	1680	1016	14.446	25.200	0.800	6.720	
Aug. 24	1140	1024	13.465	30.780	0.527	7.980	
Total for 5 days			64.197				5.303

Total nitrogen in food in 5 days	84.500 gm.
Total nitrogen excreted in urine and feces in 5 days	69.500 gm.
Nitrogen apparently stored by the patient	15.000 gm.
Amount of chlorides as NaCl in food in 5 days	58.000 gm.
Amount of chlorides excreted in urine in 5 days	50.682 gm.
Chlorides apparently stored by the patient	7.318 gm.[2]

The feces were not examined for chlorides and it is possible that a very small amount may have been present there.

It will be seen by consulting this table that there was apparently a slight retention of chlorine in this patient. The relations of the urea to the ammonia output were fairly constant throughout and practically normal.

After five weeks a partial thyroidectomy was performed under local anesthesia (cocain and novocain) by Dr. M. B. Tinker. The lower pole of the right lobe was found to extend 3 to 4 cm. below the left clavicle and behind the sternum, but the lobe was freed and removed without difficulty. A cyst containing about two ounces of colloid material was removed from the left lobe. The patient made a good post-operative recovery.

The removed right lobe was about the size of a Bartlett pear and measured 8.5 x 7.5 x 3.5 cm. It was decidedly cystic and much colloid material oozed from the cut surface. Several areas of calcification were seen in the tumor. Microscopic examination of parafin sections of the tissue placed it conclusively in the class of simple colloid goitres. I was unable to find any areas of hyperplasia of the exophthalmic type. It is particularly interesting and significant that with a hypersecretion of the pituitary gland we so often find, as in this case, a hyposecretion of the thyroid gland.

[2] The total N determinations were made by the Kjeldahl method. The ammonia determinations were made by the Schäffer modification of the Schlössing method. The chlorides were determined by Arnold's modification of Volhardt's method. Those interested can find a full description of these methods in Emerson, C. P.—Clinical Diagnosis, 2d Ed.

The X-ray examinations of the patient's hands and feet showed the typical bony changes of acromegaly. The X-ray examination of the head gave only inconclusive evidence of the enlargement of the pituitary gland.

In conclusion it seems to me that these are the important features of this case. We have here a very definite case of acromegaly associated with an enlargement of the thyroid gland of the cystic colloid type and a probable absence or atrophy of the ovaries (total absence of menstruation). I present the case merely because of the rarity of the condition and because of the interesting associated features of the case.

I wish to take this opportunity of thanking Dr. Charles P. Emerson for permission to study and report this interesting case.

CORRESPONDENCE.

THE MEAD REPRINT OF SERVETUS' CHRISTIANISMI RESTITUTIO.

To the Editor of the Johns Hopkins Hospital Bulletin.

Dear Sir: In your issue of January, 1910, page 10, Professor Osler, in his excellent lecture on Servetus mentions that the Medical Society of London's copy of "Christianismi Restitutio," by Servetus, the Mead reprint, could not be found. This was so at the time, but on July 15 I fortunately came across the volume which had been misplaced some years previously.

I am, dear sir, Yours faithfully,

George Bethel,

Registrar and Librarian of the Medical Society of London.

NOTES AND NEWS.

WARREN TRIENNIAL PRIZE.

This prize for 1910 was awarded to Dr. George H. Whipple, Associate Professor of Pathology, The Johns Hopkins University, and Resident Pathologist, The Johns Hopkins Hospital, by the Visiting Physicians and Surgeons, and the Trustees of the Massachusetts General Hospital, for his essay entitled "The Pathogenesis of Icterus."

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LISTER PRIZE ESSAY.[1]

THE LIFE AND WORK OF LISTER.

By CHARLES C. W. JUDD,

Student of Medicine, the Johns Hopkins University.

Carlyle once wrote that "Universal history, the history of what man has accomplished in this world, is at bottom the history of the great men who have worked here." These great men he calls "heroes," be they human or divine. In much the same way is the history of medicine composed. It is a history built up, like this world of ours, of the work contributed by its many heroes, whether real or legendary. Some few of these heroes are preëminent; they who have marked epochs in development, they whose work was essential to further progress, they who determined the various strata of medicine's history. Lister is one of these.

So much in the history of medicine is common educational knowledge that a hasty review of it must needs have grounds to justify such a procedure in presenting the life of one man. Lister's work, however, has such a profound bearing upon medical advancement that a clear idea of the rôle he plays in medical history warrants a brief account of those preëminent men on whose work he built.

Out of the mists of mythology in the history of medicine there emerges a first authenticated man, that gigantic Coän figure Hippocrates. Hippocrates was mortal, but his ancestry is shrouded in divinity and his training obscured by folk-lore. The famous oath of Hippocrates, sworn by his divine forebear Aesculapius[2] and Apollo, the god of the art of healing, makes these points none the less enigmatical. However that may be, Hippocrates furnished inspiration for a great branch of learning, a great field of accomplishment. He did his work well, he studied hard, he accomplished things. He healed the sick, he made keen and valuable clinical observations, some of which are still extant and living truths. He founded a great school of medical learning and gave us an ideal regimen of the physician's life.

Centuries later there stands forth a figure, also that of a Greek,[3] that dominated medicine from a period early in the Christian era until the Renaissance. This was Galen, who gave so much to the world of medicine, that for centuries that world insisted upon the unquestioned acceptance of his truth and untruth, who constructed (it is due to him to say unintentionally) a dogma as rigid, intolerant and inviolate, as that of any creed.

Galen's bulwark against advancement was, by some few,

[1] To the author was awarded the "Lister Prize," a sum of $150, offered by Dr. A. E. Malloch, of Hamilton, Ontario, Canada, according to the terms stated in the Johns Hopkins Hospital Bulletin, May, 1909.

[2] Identified with the Egyptian deity, I-em-Hetep, who was said to have lived as a healer of the sick as early as 4500 B. C.

[3] Most references state that Galen was a Roman. Though his birthplace, Pergamum, in Mysia, had been under Roman rule since 133 B. C., the spirit, tradition, language and customs of the place in Galen's time were all essentially Greek. References may be found in support of this in a "Classical Dictionary," by M. Smith —John Murray, London, 1863—under Mysia, Pergamum, Thrace, etc.; also a "Dictionary of Greek and Roman Geography," ibid., 1878.

valiantly but uselessly attacked. Among the Moors, however, some progress was made, not by attacking Galen's weak points, but by establishing their own system of medicine. Under the "régime" dominated by Galen there arose factions among medical practitioners until there came to the front Ambroise Paré, who did much to break down these prejudices and to heal the schisms that had sprung up to rend the ranks of medicine. Even he could not, nor did he try to make headway against the authority of Galen. He did, however, place surgery upon a more rational basis than the world had ever known, thereby gaining for himself the title, "The father of surgery."

Then came the period of the Renaissance, the age of terrestrial and celestial discovery and the era of the Reformation. There was a great new birth of learning, when through the gift of printing, knowledge was disseminated throughout the old world. A great new world was found when adventurous sailors took ship for "westward-ho" and a great revelation made when a daring mind dissipated the "solar myth." Then occurred the third, but first successful, "uprising of the human intellect against the spiritual domination of Rome." Medicine too had a share in the great universal reaction, for just as there arose a Gutenberg, a Columbus, a Galileo, just as in the ranks of religious teaching, there sprang up a Luther to fight against the established belief as dictated by the Pope and champion a freedom of religious thought and work, so there arose in the ranks of medicine a champion, Vesalius, who first successfully questioned established tenets in medicine; who by demonstration and anatomical findings, refuted errors based on the prerogative of Galen. The work of Vesalius, however, out-Luthered Luther, for through the efforts of Loyola,[4] "who bore in the great Catholic reaction the same part which Luther did in the Protestant movement," the prestige of Rome to-day is supreme over a half of the Christian world, while Vesalius gave the death blow to the supremacy of medical authority and brought about the dawn of empirical methods, to which the science of medicine owes its establishment.

Stirring times these were after the lethargy of the Middle Ages, times when great things were discovered, when sound data were applied in a new way. The work of Vesalius in gross anatomy was continued by scores of earnest workers, who gave their time and energy to its cause.

The reform, however, did not confine itself to the subject of gross anatomy. From this time, the advances made in all branches of medical science are legion. Independent thought became possible, the demonstration of a fact by empirical methods rather than by traditional teachings was no longer scouted and the chains of superstition and dogma were broken. Under these conditions the true circulation of the blood was established, gross anatomy and pathology were refined through the use of the microscope, the function of the nervous system was approximated, physical diagnosis and clinical observations were amplified and other scarcely less important truths were established, while many an old and incorrect supposition was refuted.

It was not only the physician who added to our knowledge, but the physicist and chemist frequently gave the very "open sesame" when further progress was barred. For instance, the processes of digestion as understood to-day are based upon a host of valuable data determined in the schools of the famous German chemists, ably seconded by the French, English, Italian and Viennese investigators of the eighteenth and early nineteenth centuries. To the chemist Lavoisier we owe the explanation of the cycle of oxygen and an understanding of the basic principle of respiration. To Volta, the physicist, we owe the rectification of Galvani's erroneous idea of nerve stimulation. The three great weapons of the physician, the microscope, polariscope and spectroscope, are gratuities of the physicist. It is the long list of such "heroes," who, following in the wake of Vesalius, transformed medicine as an art into medicine as a science.

Contrasted with this splendid advancement in other branches of medical science, surgery was woefully deficient. Some new bits of operative procedure were developed, some unnecessarily severe polities were abandoned, but surgery, in spite of the ample opportunities the manifold wars afforded for practice, was scarcely better off than in the time of that godly Samaritan, Paré, who was wont to declare, "I dressed him and God healed him." The wars and the nations produced some gigantic operators, daring, ingenious, thoughtful men, but the necessity of inflicting severe pain and the inability to conquer in the unequal war against that arch enemy suppuration, were great odds against which they had to fight. The surgeon, indeed, needed the coöperation of Providence to effect a cure. The patient, indeed, needed the waters of Lethe and the gift of Morpheus combined to overcome the horrors of an operation and the pain of a long, offensive, debilitating recovery of healing by "second intention," interrupted appallingly often by an agonizing death from septicæmia, pyæmia, erysipelas, hospital gangrene or other form of acute suppuration.

At the close of the eighteenth century nitrous oxide was discovered and Sir Humphrey Davy called attention to the peculiar effects produced upon the psychical and nervous states when that gas was inhaled. He even went so far as to suggest it as a means of making operative procedures less painful, but the surgical world let slip this golden opportunity. It fell to the lot of America to introduce a general anæsthetic into surgical practice. Though both nitrous oxide and ether were used in isolated cases a few years earlier, the honor of disclosing the practical value of surgical anæsthesia must be awarded to Warren and Morton, who by the use of ether, in 1846, first gave a successful public demonstration in Boston, of painless operating. Within a year not only was this boon to surgery generally known and utilized, but chloroform was introduced by Simpson as a general anæsthetic. Here surgery began to be revolutionized. Extreme dexterity and rapidity in the operator had been demanded when each incision was an agony for the patient. But now more thorough methods, more delicate

[4] The contrast between Vesalius and Loyola is delightfully depicted by Foster in his "Lectures on the History of Physiology," on page 8.

technique and even simple exploratory operations could be resorted to.

The giant bugaboo of the surgeon, however, still persisted. The mortality, if not the suffering under the knife, remained unreduced, for suppuration swept on unchecked. Only veterans in surgery can give an accurate or even an approximate idea of the horrors that infection produced in the great hospitals and under the hands of the most skillful operators in the days before the introduction of antiseptic surgery. According to the older statisticians, as high as 80 per cent of the major surgical cases of the great hospitals died, not from the operation, but from subsequent infection, while healing by "first intention" constituted but a small portion of the remaining 20 per cent.

The centuries-long contention as to the spontaneity of the origin of life was quiescent in the early years of the past century. This pacific state of affairs was brought about by the investigations of Liebig, who had convinced the world that microorganisms owed their origin in some strange way to the oxygen of the air. For centuries there had been a theory that certain forms of life were causative agents of disease. Some of the surgeons, acting on these combined ideas, began to attack the problem of avoiding suppuration by excluding the air with its oxygen. We can readily understand how their methods failed, but those holding firmly to the belief, maintained that their technique and not their method was at fault.

The superb work of Pasteur on fermentation not only demonstrated the fallacy of Liebig's hypothesis, but explained the failures of those experimental surgeons who would reduce infection by hermetical procedures of operating. To the latter, Pasteur's was an iconoclastic doctrine. To surgery it seemed as though even that which it had, had been taken away. So it seemed until Lister turned the defeat into victory, for Lister it was who raised Pasteur from the position of a surgical iconoclast to that of an emancipator. Lister it was who saw that the processes of fermentation as determined by Pasteur had a direct bearing upon the phenomenon of the putrefaction of wounds. Lister it was who applied this inference to surgical treatment and he who revolutionized the whole of surgery, for it may fairly be said that "active surgery, the science of operating," emanated from this induction and the introduction of antisepsis.

The year of grace 1827 brought forth no great events in the history of England, but it was a significant one in the scholastic and domestic life of one sturdy Britisher, for in that year Joseph Jackson Lister, of Upton, Essex, made his first contribution to scientific literature and his wife, Isabella, gave birth to his son, Joseph. The Listers were of good citizen stock, belonging to that peaceable sect, the Society of Friends. Though a London wine merchant by trade, the elder Lister was of a scientific turn of mind and occupied his leisure hours with microscopic observations and improvements upon the mechanical structure of the microscope. In conjunction with Dr. T. Hodgkins, he first observed the formation of the red corpuscles of the blood into rouleaux and determined the diameter of the corpuscles by means of a camera lucida. As early as 1824 Mr. Lister began work on the acromatic microscope and it was at the suggestion and under the direction of Mr. Lister that Andrew Ross made his one-eighth inch objective. In Lister's contribution to the improvement of lenses, lies his chief claim to eminence in science, but it is no mean claim, for he transformed the compound microscope from a scientific toy which distorted as much as it magnified into a powerful engine of research. The younger Lister, in speaking of his father's work says: "Numerous improvements have since been introduced, both in this country and abroad, in the construction of the acromatic object-glass, but Lister's law of aplanic foci remains the guiding principle 'as the pillar and source' of all the microscopy of the age." Scientific thought, therefore, played a large part in the heredity and environment of the boy, Joseph, who first graced the home of the wine-merchant-microscopist on the fifth day of April, 1827.

The early home training of young Lister was carefully conducted. He was afforded the advantages of refinement, high respectability of living and every benefit short of over-indulgence. Of his advantages, not the least was the opportunity afforded him for a broad, thorough education. Though his early tutelage was intrusted to a Friends' school in Tottenham, one can well imagine that the father's interest in his hobby was extended to a careful introduction of his son to the microscope and some of the wonders it revealed, long before the younger Lister went to University College.[5] Subsequently, he went to the University of London,[6] where he graduated at the age of 20 with the degree of Bachelor of Arts. For the next five years he studied medicine under the Medical Faculty of University College and in the University College Hospital. Here it was, that by his studious habits, his intelligence and his genial personality, he gained not only the interest and esteem, but also the friendship, of his tutors and professors. Chief among those whose interest Lister aroused were Thomas Graham, who occupied the chair of chemistry, and Sharpey, that great teacher of physiology, whose influence over his pupils has ever been their delight and the wonder of those not so fortunate as to be counted among their number.

Lister's earliest researches, influenced doubtless by his father and Sharpey, were directed to the fields of histology and physiology. His first contribution, written in 1852, but not appearing until a year later, was upon the histology of the contractile tissues of the iris. In this paper he verified Koelliker's previous observations upon the identity of that tissue with non-striated muscle. On June 1, of the same year, another manuscript dealing with the muscular tissue of the skin was given publication. Still later that year appeared his observations on "The Flow of Lacteal Fluid in the Mesentery of the Mouse." This was not in itself particularly important. It did show, however, his accuracy of observation and his determination to see things with his own eyes. The thoroughness with which each subject dealt with was treated, the untir-

[5] Macaulay is responsible for a delightful defense of this institution and a description of the environment it afforded.

[6] University College was not, until many years later, incorporated in the University of London.

ing energy with which each investigation was pursued from its undertaking to its completion, induce one to believe that the words of his future friend, John Brown, were inspired by Lister's own example: "You come to the chest of knowledge. It is shut, it is locked, but . . . . you have the key, put it in steadily and home. But what is the key? It is the love of truth; neither more nor less; no other key opens it; no false one, however cunning, can pick that lock; no assault of hammer, however stout, can force it open, but with its own key, a little child may open it, often does open it, it goes so smoothly so with a will." It was with this key that Lister attacked each problem.

This series of experiments and the careful reports he published describing them, placed Lister in the field of original investigators. It is not, however, to be concluded that he devoted his time exclusively to laboratory research. On the contrary, his most active work was in the hospital, for he served as dresser to, and later as successor to Henry Thompson, as house surgeon, under Mr. (afterwards Sir) J. E. Erichsen.

Upon leaving University College Hospital in 1854, Lister, heeding the advice of Sharpey to "take six weeks of Syme's clinic," went to Edinburgh and started work under that kindly Christian gentleman and famous surgeon, who was considered "the safest operator of his day." These six weeks grew into as many years, the first two spent as acting resident surgeon to Syme, and the remainder as assistant surgeon in the Royal Infirmary, Edinburgh.

It is a fair presumption that it was not only Syme's clinic that prolonged Lister's residence there, but that Syme's daughter played no small part in making his sojourn a question of years. In any case we learn that Lister's share in the social coterie of Syme's assistants, famous pupils and cultured friends was not the least, and that he was not long in winning his teacher's daughter, Agnes, as his wife.

These were happy years in Edinburgh, happy in the intimacy they gave him with the frequenters of Syme's hospitable household, of which Lister was for a time an inmate, happy in the companionship of the great master himself and happy too in work well performed. Dr. John Brown, the Holmes of Scotland,[7] we know well as one of the number of frequenters of Syme's household. Brown's friends (including Sir Walter Scott, Lord Erskine, as well as "Wee Marjorie Fleming" and a host of others) his kindness, his refinement, his culture and his genius, give the cue to the delights this house afforded. In his "Marjorie Fleming"[8] will be found a sketch from which one can picture what Lister's social and domestic life must have been, while in "Rab and His Friends"[9] one has an indelible glimpse of Syme as a man and as a surgeon. This same little story of "Rab" also depicts the prevalent tragedy in surgery in the days before either anæsthesia or antisepsis came as priceless gifts to surgeon and patient. John Brown was not alone though, for many a "Savant" had a share in the Syme's entertaining. Famous surgeons from all parts of the kingdom and from the continent made Syme's clinic their Mecca and found their way most readily to share in his open hospitality. Men of letters and diplomats were no less welcome. Here it was that Lister became associated with many of the distinguished men of the day.

The relation between Syme and Lister was not merely that of master and pupil, nor was it confined to the still more intimate family connection established by Lister's marriage. There was always the highest esteem in the mind of each for the integrity of soul and surgical ability of the other. Syme never tired of speaking in the highest terms of Lister's ability and in prophesying a great future for him through his application of science in general to his profession, while in procedures of operating, Lister invariably gave the credit to the training he received under the intrepid Scotch surgeon.[10] We learn too that in the operating room, "he (Lister) did some brilliant and daring work with Syme."

However exacting Lister's work may have been in the wards and surgery, he made time for other activities. It was in Edinburgh that Lister began his career as a teacher, holding the position of extra-mural lecturer on surgery. Annandale, one of his pupils during this time, states, that from the very beginning his many original and interesting suggestions in connection with histology and surgical pathology made his course popular with the most diligent and capable students and that, moreover, these suggestions, looked back upon from the present state of knowledge, were the forerunners of the important investigations leading up to the introduction of those great antiseptic principles which have revolutionized surgical practice.

Into original investigation Lister threw himself with his accustomed energy and painstaking care, for combined with his love of truth he possessed the traits of patience, persistence and sustained concentrated attention in the working out of details. Illustrative of this, it may be noted that he followed up his earlier investigations on the histology of non-striated muscular tissue by a report before the Royal Society in 1857 "On the Minute Structure of Involuntary Muscular Fibre." Another instance of this habit of mind may be found in the fact that his previous study of the viscera[11] led him to make further investigation into the physiological functions of certain visceral nerves. This, in turn, stimulated inquiry upon nerve-trunk morphology. An isolated study, which deals with the "Cutaneous Pigmentary System of the Frog," remains to-day

[7] Some six or eight weeks after the association of these two personalities occurred to the author, an editorial in the August 28, 1909 edition of the Journal of the American Medical Association, drew a similar comparison between the two men.

[8] Spare Hours, by John Brown, M. D., second series, pages 51-80, Houghton, Mifflin & Co., Boston, 1884.

[9] Spare Hours, by John Brown, M. D., first series, pages 393-413, Houghton, Mifflin & Co., Boston, 1884.

[10] Syme's influence upon Lister is beautifully illustrated by a comparison of the former's "Excision of Diseased Joints" (1831) and Lister's great surgical paper, "Excision of the Wrist for Caries" (1865).

[11] "Observations on the Flow of Lacteal Fluid in the Mesentery of the Mouse."

one of the few important contributions to the subject. In pathology he began the study of the early stages of inflammation, which though not so extensive, or complete as the entire theory as later promulgated by Cohnheim, yet conforms closely to many of the observations made by that pioneer in the modern conception of the phenomenon. It was in this period too that Lister began his researches upon coagulation. The first challenge of Richardson's theory, that the coagulation of the blood was due to the liberation of ammonia, was made by Lister as early as 1858, when he determined that coagulation in the blood-vessels was due to injury to them and not a dissociation of ammonia from the blood. Conversely he showed that the integrity of the vessels was the means whereby the blood was normally free from coagulation while in circulation and that this condition was not due to the blood's combination with ammonia.

Made professor of surgery in the University of Glasgow in 1860, Lister went to that city and the following year was also elected as a surgeon to the Glasgow Royal Infirmary. He and his students in the University continued his previous investigations on the coagulation of the blood. Lister applied himself to the development of this problem with the assiduous care, faultless logic and keen observation so characteristic of all his research work. To this end he devised elaborate experiments, an account of the results of which culminated in the address delivered as the Croonian Lecture of 1863. This was the *nemesis* of the accepted ammonia theory of coagulation. Moreover, it enunciated the idea that foreign substances hasten the action of coagulation. "The lucidity and logical power in the conduction of his many ingenious and delicate experiments to overthrow this well-established theory entitles Lister to no small station among the English physiologists who have from the beginning been leaders in the phenomenon of blood coagulation." This comment, appearing in a contemporary number of the "Lancet," is a very just estimate of this work. This much may be said in the present state of our knowledge, about the influence of the first great product of Lister's genius: that it set at naught an erroneous though well-established theory on the phenomenon of coagulation and described accurately many details of that phenomenon upon which the prevailing opinion of the process is based.

The study of wound-dressing is still a question of vital interest to surgeons, while its development constitutes one of the most fascinating fields in surgical annals. It was Lister's part in this development that has placed his name among the immortals of medical history. While in Glasgow, particularly, Lister was impressed with the frightful prevalence of suppuration in wounds and its consequences. "In contrast to his associates, he manifested a profound discontent with things as they were." The frequent occurrence of infection in compound fracture, and its absence in simple fracture, was an observation that struck keenly the discriminating mind of Lister. Basing his opinion upon his previous investigations, Lister believed that the primary cause of such suppuration in compound fracture and in wounds in general was the decomposition of the blood and serum they contained, brought about by some gaseous constituent of the air. On empirical grounds he insisted on scrupulous cleanliness on the part of his dressers and himself in all his surgical work, using ofttimes deodorant solutions. His wards, however, seemed little if any better for this precaution in the avoidance of infection.

Lister deserves no great credit for the employment in this manner of deodorant lotions; the policy had precedent, since for many decades and even centuries, substances now known to possess decidedly antiseptic properties had been known and used as cleansing lotions in medical practice, in the same way that Lister used his deodorant lotion, certainly with little effectiveness and with no more sound basis of reason. Astonishing guesses at both antisepsis and asepsis are numerous in the archives of surgical literature, but the fact that they were mere conjectures, and not rational deductions, has lost them their place. A single example will suffice to account for their failure to gain recognition. It is told of Coldbatch that he used a paste composed of boracic or salicylic acid for local application to wounds, but as a solvent he used indifferently water or urine! Of those who more wisely surmised probably none is entitled to so much consideration as Semmelweis, who, though no more guilty of a knowledge of the microbic origin of septic poison than our prehistoric forebears, though ignorant of any application of his method to surgery, still used in his obstetrical practice a strong antiseptic lotion for cleansing his hands as a prophylactic measure against puerperal contagion. When, however, this forgotten method, used as early as 1847, was brought to Lister's attention in 1883, he thenceforth regarded Semmelweis, whose work had been repudiated by the profession, as in some measure his forerunner.[12]

While Semmelweis was sinking into oblivion, a young scientist of France was coming to the front. The connection between the work of this scientist, Pasteur, and Lister is too close to permit of any satisfactory account of one without something more than passing reference to the other. Primarily a chemist and physicist, but scarcely less a biologist, Pasteur had already laid the foundation on which Emil Fischer later built his extraordinary structure on the constitution of the sugars. This foundation was the determination of the phenomenon of physical isomerism and the introduction of stereo-chemistry, based upon the classical investigation into the crystallography of tartaric acids. Commercialism immediately made use of Pasteur for a certain alcohol manufacturer, M. Bigo, experiencing difficulty in his fermentation, employed Pasteur to determine the cause of the "oxygen"

[12] Dr. Theodore Duka, a Hungarian physician, after bringing the claims of Semmelweis to Lister's attention, wrote a small monograph, in 1888, entitled, "Child-bed Fever, Its Cause and Prevention—A Life History" (of Semmelweis). This was published in 1892 by Austin & Sons, Hertford. Last year, a more extensive biography, by Wm. J. Sinclair, published at the University Press, Manchester, appeared (reviewed by the Journal of the American Medical Association, Vol. 53, page 2032). Though both extol the greatness of Semmelweis, they fail to show that he did more than wisely surmise what Holmes surmised and brought before the profession, and what Lister did not guess—but proved beyond peradventure.

being deficient in his vats. Brewers and alcohol manufacturers, as well as scientists, imbued as they were with the doctrine of Liebig, thought that fermentation was a chemical and not a vital change. So Bigo employed Pasteur. Well for Bigo, well for the world at large that he selected the right man! It was the result of the pursuit of this problem that Pasteur gave the world the knowledge that fermentation is due to microbic contamination and the sentence "La génération spontanée est une chimère." The subsequent work of Lister, which was actuated by this discovery, undoubtedly had a marked effect upon Pasteur's later investigations. These resulted, in 1880, in the first isolation of the causative agent of an infection and its attenuation in virulence for purposes of inoculation in the production of an immunity. It may justly be said that Lister would never have conceived his idea of antisepsis without Pasteur. On the other hand, Pasteur, without Lister's work, may well have overlooked the application of his discovery as a factor in the etiology of disease, along which line his entire attention was directed thenceforward to the inestimable benefit of the industrial arts and medicine.

The advent of Pasteur's work on fermentation, coming as it did at a time when suppuration and its consequences was a theme so near to Lister's heart, was immediately coupled in his mind with an observation made in Carlisle in 1864, where carbolic acid was used as a deodorizer in the sewage. It chanced that certain cows pastured there were freed from protozoa, which up to that time had infested them. Lister's thought was, to quote from a paper read by him years later: "If the wound could be treated with some substance which without doing serious mischief to the human tissues, would kill the microbes already contained in it, and prevent the further access of others in the living state, putrefaction might be prevented however freely the air with its oxygen might enter." Carbolic acid appeared best suited to serve this purpose. His first application of this idea, in 1865, was tried in the treatment of compound fracture. His first case was a failure, but further attempts with more elaborate precautions justified his theory. His method was to wash out the wound with undiluted carbolic acid, which with the coagula made a paste. This was allowed to remain in the sore. Well overlapping the area of injury, he applied a dressing saturated with carbolic acid which was kept in place and adherent to the limb by a piece of block-tin. Over this were applied the splints and bandages. Each day, until deep healing was obtained, this dressing was renewed. In the later stages, to avoid undue irritation from the antiseptic, other dressings less irritant were applied. The result of this method led to healing as uninterrupted as in the case of simple fracture. With these results as a basis to justify his procedure, in August, 1867, Lister promulgated his fundamental idea in an address at Dublin, before the British Medical Association: "In the course of an extended investigation into the nature of inflammation and into the healthy and morbid condition of the blood in relation to it, I arrived several years ago at the conclusion that the essential cause of suppuration in wounds was decomposition, brought about by the action of the atmosphere upon the blood or serum retained within them, and in the case of contused wounds, upon portions of the tissue destroyed by the violence of the injury. To prevent the occurrence of suppuration, with all its attendant risks, was an object manifestly desirable, but till lately apparently unattainable, since it seemed hopeless to exclude oxygen, which was universally regarded as the agent by which putrefaction was effected. But when it was shown by the researches of Pasteur that the septic properties of the atmosphere depend not upon oxygen or any gaseous constituents, but upon minute organisms suspended in it, which owed their energy to their vitality, it occurred to me that decomposition in the injured parts might be avoided without excluding the air by applying as a dressing some material capable of destroying the floating particles."

This paper gave rise to an avalanche of criticism—criticism of incredulity—as to the efficacy of the method and criticism of non-priority in the use of phenol for this purpose. Through his application of the sciences to his work, Lister was so far ahead of his own day that such censure is not surprising. Even at the time when he went to London many years later, opposition to "innovations" was so strong in examining boards there, that the younger students, those who would have served best in giving impetus to the new method, were skeptical and afraid to adopt and defend "Listerism." Again the tentative use in surgery of chemicals with antiseptic properties by such men as Bassi, Semmelweis, Lemaire, Bottini and others, before Lister's advocacy of carbolic acid, gave some ground for the claim of non-priority. Even so distinguished a surgeon as Sir James Y. Simpson[13] (no other than he who introduced acupressure as a hæmostatic agent and chloroform as a general anæsthetic) bitterly attacked Lister upon these grounds. His error lay in this: that he failed to discriminate between a mere surgical dressing and a basal principle underlying a whole surgical system, between bland empiricism and strict scientific deduction.

Quite the antipode of Pasteur, who vehemently defended each questioned hypothesis which he propounded, Lister was always dignified in the espousal of the great truth he offered the world. A few months after his Dublin address he thus defended his discovery, clearly defining his claim to priority as being based, not upon the use of phenol, but upon the theory of antisepsis: "I may repeat that I never claimed to be the first to use carbolic acid in surgery. The success which has attended its employment here depends not so much on any specific virtue in it, as on the wonderful power of recovery possessed by injured parts when efficiently protected against the pernicious influence of decomposition. I selected carbolic acid as the most powerful of known antiseptics; but I think it not unlikely that my object might have been gained by using on the same principle some familiar disinfectant." He further stated that it was not to be expected that carbolic acid would act as a charm, but that whether this agent or some other of analogous properties was employed, it was only by the

[13] Simpson's was a pugnacious spirit. Vide, "Sir James Y. Simpson," by Dr. L. Gordon, in "Masters of Medicine Series," New York, Longmans, Green & Co., 1898.

light of sound pathology and strict attention to practical details that the full measure of magnificent results which the antiseptic treatment was capable of affording could be attained.

Far more potent than words coming from the pen of Lister, however, were the works of the great man in establishing his sound principle upon a firm basis. Henceforth his object was to demonstrate the logic of his conclusions, to show that these conclusions were invaluable to the science of operating and to simplify his technical method of excluding contamination to such an extent that there might be a minimum of irritation to the tissues consistent with absolute safety against suppuration. Having satisfied himself as to the reliability of his treatment of compound fracture, he next turned his attention to the treatment of large abscesses. His method was to incise with antiseptic precautions, cleanse and apply a putty of phenol, linseed oil and carbonate of lime—a compound devised by himself to take the place of the natural putty formed of phenol and coagula. This technique yielded brilliant results and promoted rapid healing without constitutional disturbances.

The astute observations of the pathological phenomenon of healing in these wounds led Lister to his next innovation.[14] He observed that under antiseptic conditions, injured tissues of a wound, instead of sloughing served as a pabulum in the process of repair, were later absorbed and finally supplanted by living tissue. Even dead bone was seen to be thus replaced by healthy osseous material. Absorbable substances had been used as ligatures decades before, but owing to their causing suppuration, which led to secondary hemorrhage, their employment had been summarily discarded. Lister was convinced that these failures were due to the septic condition of the material used for ligation. By a process of "philosophical induction" from his observations on antiseptic repair, he concluded that a material of animal matter, strong, soft, pliable and free from contamination would form a successful ligature. For this purpose he employed prepared cat-gut. Careful experiments were devised by him to treat this in such a manner as to free it from contagion and still retain its physical characteristics. Its disadvantages were that the sterilizing process required considerable time to complete and the ligatures would occasionally undergo too rapid absorption. To obviate this delay and control the lysis, many years later he devised an improved method, where, by chromatizing his material he obtained especially good results without loss of time and without increasing the chance of inducing sepsis or hemorrhage. Even with the first method of preparation, animal experimentation convinced him of the efficiency of this substance as an absorbable ligature. In the application of it to surgical practice he observed that the ligatures about the vessels became absorbed and replaced by a ring of living tissue, that this procedure obviated the use of long threads and did not require removal with its attendant pain to the patient and danger from hemorrhage. To this conception and these experiments are due a simple measure which is still frequently and efficaciously employed in surgical routine.

The development of asepsis from antisepsis as promulgated by Lister has been and still remains a field of rather bitter controversy. Some few strenuously maintain that to Lister belongs none of the credit of aseptic surgery. The vast majority, however, see in asepsis but a development, a natural evolution of Lister's antiseptic management of wounds. Surely antisepsis, in its wider sense, embraces asepsis. The latter is applicable only to some injuries inflicted by the surgeon, the former alone is adequate in the surgical treatment of accidental trauma, while both have as their underlying principle the exclusion of pathogenic bacteria from open wounds. With these details in view, any controversy as to the origin of either system would indicate that the pendulum of condemnation has swung beyond the point of wisdom, that the zeal for asepsis, like most reactions, has gone too far. Convinced of this, Championnière states that "aseptic surgery is as much an issue of the discovery of Lister as is true antiseptic surgery." To establish a contiguity between asepsis and antisepsis would undoubtedly give added support to this statement. In some measure there is a connecting link in the prophylactic treatment of infection by the increasing employment of such agents as hexamethylenamine in both medicine and surgery, silver compounds in the ophthalmic treatment of the new-born and the like.

The evolution of asepsis from antisepsis, moreover, was forwarded in large measure by Lister himself. Therein lies the greatest claim to the soundness of Championnière's statement. It was during Lister's residence in Glasgow that he called attention to the "aseptic" condition of wounds after antiseptic treatment and emphasized this condition as the one striven for. From this early date he believed that an antiseptic was injurious to the cellular elements of the body as well as to the microorganisms and that the aim of the surgeon should be in its employment in sufficient but not in excessive amounts. To this end he began measures for the reduction of the inflammation caused by the application of antiseptics and instituted investigations into the pharmacological action of the drugs used for this purpose. He commenced decreasing the concentration of solutions used. He also introduced a protective plaster of prepared oiled silk rendered aseptic by the use of antiseptics. This he applied next to the wound, over which the active antiseptic plaster was spread. As the result of this investigation into the action of phenol, he first formulated the now well-known pharmaceutical law that "the energy of action of any substance upon the human tissues depends not only on the proportions in which it is contained in the material used, but also upon the degree of tenacity with which it is held by its solvent." This property he utilized by combining phenol with an organic vehicle. The antiseptic was thus rendered less irritating to the tissues, because in this combination the phenol was liberated slowly and yet the energy of action was sufficient to form an effectual bulwark against the invasion of bacteria. This account affords

[14] Vide "On Some Points in the History of Antiseptic Surgery," Vol. 2, page 395, "The Collected Papers of Joseph, Baron Lister." This whole letter is most valuable in displaying the early evolution of antiseptic treatment as it occurred to Lister's mind.

an outline only of the innumerable improvements made by Lister over his earlier method, all of which had the one object; to simulate as far as possible in his treatment of open wounds, the conditions existing in simple fractures. His conscious aim was asepsis. His approaches to it in practice, however, were gradual, as he was loath to adopt any method which he considered had in it any element inconsistent with absolute safety. In 1890, in speaking of this aspect, he states: "I have not ventured to make the experiment (asepsis) on any large scale, though I have long had it in contemplation. It is a serious thing to experiment on the lives of our fellow men, but I believe that the time has now arrived when it may be tried, and if it should succeed, then perhaps would be fulfilled my early dream. Judging from the analogy of subcutaneous injuries, I hoped that a wound made under antiseptic precautions might be forthwith closed completely, with the line of union perhaps sealed hermetically with some antiseptic varnish, and bitter was my disappointment at finding that carbolic acid induced by its irritation such a copious effusion as to necessitate an opening for its exit; hence came the drainage of wounds. But if we can decrease the use of an antiseptic substituting aseptic and non-irritating materials in the operation, we may fairly hope that the original ideal may be more or less attained."

Lister left Glasgow in 1869 to assume the chair of clinical surgery at the University of Edinburgh made vacant by Syme's retirement from active work. Syme died the following year. In spite of his appreciation of Lister's genius and his advocacy of the younger surgeon's methods, the principle of antiseptic treatment was practically unknown to the students at the University. Lister sought to teach them by means of the observation of phenomena, to appreciate not only the value of his doctrine and discoveries, but also, as he says, using John Brown's phrase, "the value of the love of truth." [15]

To rest upon his discovery was not Lister's method. To perfect what he had already accomplished, to observe and to explain his observations, to get at the very underlying principles governing his doctrine; these were the results at which he aimed. To this work he brought a capacity for the practical application of all means at his hand which would accomplish his ends. An example of this adaptability was his introduction of the "carbolic spray" to sterilize the air about the field of operation. This mechanism he perfected from time to time, finally employing steam to effect the atomization of a dilute solution of phenol, which was thus diffused throughout the atmosphere, rendering, as he thought, the operating room sterile. This was not finally discarded by him as being unnecessary until 1887, though six years before he began to doubt the need of this precaution. It is not to be denied, indeed it should be insisted upon by those who wish to have Lister's work given a just valuation, that in the early days he labored under the misapprehension that air was the chief medium through which poison was brought to wounds, though he recognized then and with ever-increasing conviction that all foreign materials, ligatures, instruments, skin, clothing, etc., were contagion carriers. Finally he expressed himself thus: "I was led to conclude that it was the grosser forms of septic mischief rather than microbes in the attenuated form in which they existed in the atmosphere that we had to dread in surgical practice." Lister's unnecessary prudence with reference to atmospheric infection, like his hesitation in abandoning the use of antiseptics for asepsis, is indicative of his elaborate precautions against the access of microbic contamination. Granting that they were both errors, still they were on the right side and illustrate Lister's fundamental principle in the treatment of his cases: "Let the thing tried be that which, according to our best judgment, is the most likely to promote the welfare of the patient."

The investigations pursued by Lister during his second residence in Edinburgh into the bacteriological and chemical nature of various antiseptics is of importance. Carbolic acid had been found satisfactory in that it was efficient, but it produced an undesirable irritation. Boracic acid having found favor with some surgeons, Lister subjected it to a searching study. He determined that even concentrated solutions were not always reliable. On boiling, however, he found that a considerably greater degree of concentration could be obtained and that gauze impregnated with this hypertonic solution made an efficient dressing for infected wounds without causing undue irritation. Carbolic gauze, salicylic acid, zinc chloride and other chemicals were likewise given a thorough investigation to determine their relative antiseptic properties. Though not intolerant in any degree of other antiseptics, Lister, in the light of his own researches, remained faithful to phenol, until finally, in London, by his ingeniously devised methods of standardizing the bactericidal properties of chemicals, he adopted mercury compounds as being the most efficient in non-irritating concentrations. Of these he used the bichloride first, though later he advocated the double cyanide of mercury and zinc.

Lister's surgical cases in Edinburgh afforded a significant phenomenon which did not escape his observation. He noted that any darkening of the protective plaster used in his dressing of wounds was, when accompanied by odor, an indication of sepsis. But two anomalies were also noticed, namely, that sometimes this evidence of sepsis occurred without local or constitutional disturbances, and on the other hand, that local and constitutional disturbances sometimes appeared without attendant darkening of the dressing. How could this be explained? At that time fermentation and suppuration were not known to be distinct phenomena. Specific bacteria were not recognized as causative agents in the various forms of suppuration. The ignorance existing concerning these two facts is not in the least surprising, seeing that the science of bacteriology was but in embryo. In spite of this lack of established data, Lister suggested that the various forms of putrefaction, pyæmia, gangrene, etc., and even modifications of these troubles might well be due to different orders of micro-

[15] Osler, in the Harveian lecture, 1906, states that Lister is one largely instrumental in "The Growth of Truth."

organisms, thus more than hinting at what are now known as "mixed" infections.

Through the application of his methods the conditions in surgical hospitals were completely changed. Several lectures on the salubrity of those institutions where his methods had been adopted, pointing out their transformation from hot-beds of pestilence to "models of healthiness," gave great impetus to the propagation of the new truth on the continent. The brilliant work of his pupils abroad must not, however, be overlooked in this connection. Saxtorph and Bloch, in Denmark, and Championnière, in France, had already made their influence felt in the diffusion of Lister's doctrine. During the Franco-Prussian War, Lister wrote a pertinent paper on the application of his tenet to military surgery, but the authorities in Germany were somewhat dilatory in its application. Thiersch, Volkmann, von Miculicz and other pupils of Lister, however, soon made their impression upon surgical thought and practice.[16] When Lister made a tour on the continent in 1875, his progress was marked by an almost triumphal procession. In Leipzig and Munich great festivals marked the occasion of his presence. Clinics were held by von Langenbeck, Thiersch, Volkmann and others to demonstrate the success of the master's genius. He was hailed as a "savant" and benefactor. In all those hospitals where antiseptic measures had been adopted, he found the pest of suppuration a stranger. On the continent the achievements of his genius were recognized and he himself appreciated, success was attained and recognition secured —rewards granted to so few great discoverers before their death.

After considerable deliberation, Lister accepted an offer, made in 1877, of the position as clinical surgeon to Kings College, London. Even at that date his tenets had not secured universal recognition throughout England, due in large measure to "heartrending" failures of operators less painstaking than himself. It was in the hope that from this larger center he might more successfully spread the great truth of his discovery that he was finally induced to leave Edinburgh.

To ascertain the validity of his conception of the specificity of microorganisms in the production of "various complications of wounds" and further to corroborate his basal idea of microvital changes in the production of fermentation, Lister, sometime before he left for London, began work of a bacteriological character. By the time of his departure from Edinburgh he had, with technique worthy of Koch, isolated the "*Bacterium lactis*." The account of this investigation and the results obtained he delivered as his opening address, when he assumed his new position. In this paper he epitomized Pasteur's teachings, amplifying them with new information derived from his own researches, which showed that milk had no inherent tendency to undergo lactic acid fermentation, but that it underwent this transformation rapidly when the specific "*Bacterium lactis*" flourished. From these facts he drew the conclusion that this property of fermentation must be kept in mind in regulating sanitary conditions in hospitals; that the greatest care must be taken to prevent the growth of the specific microorganisms causing sepsis.[17] This work was no small achievement, for it was probably the first isolation of a single microorganism having a specific action. Moreover, it gave added support to his conception that many and not one variety of microbes are concerned in the various processes of suppuration. Other papers along these lines appeared in the next two years, both on the special relation of microorganisms to fermentations, inflammations and diseases, and also their general relation to pathology. The facts disclosed by these investigations and the deductions made from them did not, however, obscure Lister's insight into the true nature of disease, for, quite in harmony with the teaching of to-day,[18] he maintained that some but not all inflammatory conditions were attributable to the baleful influence of bacteria. Indeed, he even went too far, for Dr. Welch, by his discovery of the *Micrococcus epidermidis* as the causative agent of "stitch abscess," set right an error made by Lister when he assumed that this lesion had as its sole etiology, anæmia, caused by too tight a suture.

As has been noted, the physiological and pathological properties of the blood had been, since Lister's first residence in Edinburgh, a field towards which he had often directed his efforts. In 1877 he observed that blood secured under antiseptic conditions neither clotted nor fermented. Hence he concluded that blood in itself had no inherent tendency to putrefy. Four years later, as an elaboration of this idea, he delivered a most suggestive paper demonstrating that intrinsically the blood had antiseptic properties. He obtained uncontaminated extra-vascular blood which remained sterile despite the addition of small amounts of putrefying material, thus demonstrating that, as he expressed it, "bacteria per se are unable to grow in normal serum and can only develop in that liquid when it has been vitiated, whether by the addition of water or the active products of putrefaction." This protective action he attributed to the serum and more particularly to the "pus cells," which he described as "rapidly peopling the lymph with vigorous new living elements." The importance of these observations can scarcely be overestimated, for they formed the common "anlage" from which were developed the two theories of immunity as conceived by Metchnikoff and by Ehrlich.

It may possibly appear that too much space has been occupied in setting forth Lister's work as an investigator and too little devoted to his other achievements. It was, though, by his work as an investigator that he gave surgery its most powerful weapon, while many an operator has done very reputable work, comparable in many respects, to that done by Lister. He was, however, a pioneer in many modern operations. Relying upon the assistance of antisepsis he dared to

[16] The Lancet, for October 11, 1884, has an editorial which would indicate that this grew to such an extent in Germany, that at that time it was held as malpractice not to employ "Listerism," in surgical treatment.

[17] "Just as the various fermentations had each its special microbe, so it might be in the various complications of wounds."

[18] Adami: Medical Record, March, 1896; ibid., Keen's System of Surgery, 1908; ibid., Principles of Pathology, 1908.

venture upon forbidden ground; to open and drain psoas abscesses, to explore joints and to perform osteotomy for the correction of deformity. His idea of wiring ununited fractures (patellar suture is a striking example of this) is a very valuable contribution. To him, also, we owe the successful revival of suprapubic cystotomy. Though in the treatment of mammary carcinoma his measures were not so radical and hence so successful as Halsted's, still to him must be given the priority in the removal of the axillary contents in the treatment of this form of tumor, an operation, according to Sir Hector Cameron, first performed by Lister in 1857. These and many other operations are attributable to his surgical ingenuity. They are ordinary procedures in our day. Their importance lies in the very fact that they still remain accepted surgical tenets and have led to many of those improvements which have created modern operative surgery.

As a teacher scarcely less than as a surgeon, Lister has left a name to be revered. "Intense loyalty" has been the universal homage paid him by his pupils and assistants. Aside from the great truths he gave his disciples, he had that priceless gift of stimulating enthusiasm among those who came under his personal influence. To those less fortunate, the plain lucidity and forcefulness of his contributions to medical literature afford an echo of his inspiring personality.

The sciences relative to medicine gained an impetus under the influence of Lister that is almost incredible. That of bacteriology, though not created by him, was surely elevated to its now important place by his demonstration of its application to the etiology of disease.[19] With the introduction of antisepsis all sciences requiring animal experimentation (physiology, pharmacology, physiological chemistry, etc.) were advanced in so great a degree that it is scarcely an exaggeration to state that the recent brilliant results obtained in these branches are due indirectly to Lister. With hardly an exception, all branches of medical practice have benefitted by the incorporation in them of Lister's theory of contagion and his principle of the prevention of suppuration.

To enumerate the honors, degrees and titles borne by Lister would make no small catalogue. Without going into detail, suffice it to say that the Royal Society has proffered him its highest honors, and the leading institutions of two continents, as well as Great Britain, have showered degrees upon him. He has been raised to the British peerage and is the recipient of foreign scholastic titles. More striking than these honors is the estimation in which he is held by the civilized world in its appreciation of what, by his direct and indirect efforts, he has bequeathed to mankind.

In 1893 Lister retired from his active position in King's College, becoming professor emeritus of clinical surgery and consulting surgeon to King's College Hospital. Three years later he retired from all practice, but not from scientific work, for some exceedingly suggestive contributions have come from his pen since then, notably that on "The Parasitology of Malaria." In the parlance of Hippocrates, it has been granted Lister "to enjoy life and the practice of his art, to arrive at a ripe old age honored, appreciated and revered," while his works will remain as a perpetual memorial of his devotion to mankind, to science and to his profession.

If this outline of Lister's achievements places his example on such a high plane that it can afford only an ideal, the absolutely unattainable, then indeed has the rehearsal been in vain, for surely in the life-work of Lister there is much that the young physician may find to emulate. There is unquestionably a ground upon which even the mediocre devotee of medicine can build to advantage. Even he can follow in some degree the plan pursued by Lister. To draft an uninterrupted sequence in one's work after there has been laid a substantial foundation on which to build; this is within the power of all. Look to Lister's life and see the striking consecutiveness of his work. See how his physiological observations chiefly on coagulation, followed by his pathological investigations into the nature and progress of inflammation, were, each in their turn, direct precursors in his mind of the relationship of microorganisms as a cause of surgical and traumatic inflammation; this leading to his ultimate and crowning feat of devising a method for the prevention of their access to wounds. Again there still remain opportunities as many and great as in his day for the cause and prevention of many an evil genius of Hygeia remains unsolved. Finally, he did not create antiseptic surgery suddenly and without means at his hand, for the way was already blazed by invaluable scientific facts. Leeuwenhoek, Schultze, Schwann, Schröder, Dusch[20] and others, but above all, Pasteur, had by their several contributions proved that all fermentations and putrefactions are due to ever-present microorganisms. Lister insisted time and again that he but seized upon Pasteur's discoveries and applied them to surgery. But he seized them because he was watching on the mountain tops. It was because of this, that "in the hot-fit of life, a tip-toe on the highest point of being, he passed at a bound onto the other side," where others had not been. And Lister was on the mountain tops because, practitioner though he was, he saw the value of the sciences. He turned for the accomplishment of his aim towards the domains of physiology, of pathology, of chemistry, of physics and of botany.

So it is that Lister carries us far. Better even than his inestimable gift to operative surgery, he teaches us by his methods of work that it is only by the assimilation of all cognate branches of learning; that it is only through the science of the relation of all knowledge to the necessary ends of medicine[21] that the profession is to gain in power and purpose; that by these means alone will the science of medicine of

[19] Ernst von Meyer ("History of Chemistry," page 593) confirms this statement.

[20] The introduction of "The Collected Papers of Joseph, Baron Lister" tells of the work each of these performed in the annihilation of the theory of abiogenesis.

[21] Kant, in his "Critique of Pure Reason" (translated by Müller), Vol. 2, page 719, defines Universal Philosophy—his "Conceptus Cosmicus"—as "The science of the relation of all knowledge to the essential ends of human reason."

to-day, arising out of the ashes of the art of medicine of yesterday, be further evolved into the philosophy of medicine of to-morrow.

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DECUSSATION OF THE PYRAMIDS—AN HISTORICAL INQUIRY.*

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It may, I think, be said that the first step in cerebral localization, based on actual observations, was that an injury to one side of the brain caused effects on the opposite side. How early this was known I do not know, but Hippocrates (460-377 B. C.), in his "Injuries of the Head,"[1] says: "And for the most part convulsions seize the other side of the body; for if the wound be situated on the left side, the convulsions will seize the right side of the body." This fact came later to be known as the law of "crucial conduction," and is in its broad sense universally accepted at the present time. Although this crossed association attracted the attention of a number of the ancient writers, and gave rise to some speculation, still it was not accepted as proven until well into the last century.

The development of our knowledge in regard to the simple fact of the passing of the fibers from one side of the brain to the other, particularly in regard to our first knowledge concerning the decussation of the pyramids, is my present interest.

Classical writers speculated much as regards the functions of the various organs of the body, and, of course, of the brain and its activities. It is not necessary before this audience to review the many opinions that were held. These were colored by the philosophy of the individual writer, and were usually only in a very slight degree based on actual anatomical knowledge.

Galen (130 A. D.) had, as you will remember, a fairly clear idea of the nerves and of the importance of the brain. He had reverted from the doctrines of Aristotle, who considered the brain as a moist, cool organ, which controlled the ardor of the heart, back to the older views of Hippocrates and Plato, that it was the seat of sensation, motion and of the intelligence. He made dissections of many animals and a number of experiments, and seems to have known nearly as much about the brain as Vesalius and Willis did.

Galen saw clearly that local disturbances of the nervous functions must depend upon focal disease of the nervous system, and he pointed out that to obtain a knowledge of these, clinical observation must be combined with careful anatomical and experimental investigation. It was to elucidate the question of paralysis that he[2] experimented on the spinal cord. He discovered that a total transverse section of the cord caused a total paralysis below it, that a hemi-section caused paralysis of the same side, and that a longitudinal division had no effect. He argued that as all voluntary power and sensation were derived from the brain, a total abolition of

* Read before the New York Neurological Society, April 5, 1910, and the Johns Hopkins Hospital Medical Society, April 11, 1910.

[1] Adams' Translation, p. 386.

[2] De locis affectis, lib. III, cap. XIV. De anatomicis admonstrationibus, lib. VIII, sec. 6.

these functions, as in apoplexy, indicated a lesion of this organ, but that a local effect, as in the arm or leg of one side or portions of these, as in paralysis, pointed to the spinal cord. When the face was involved, the disease must be in the brain, for the muscles of the head receive their nerves from this organ.

In these sections referred to, Galen does not mention the crossed effect of the brain. He seemed to regard the brain as acting as a whole, and to think that the functions were not segregated until they were distributed to the parts of the body through the spinal cord and nerves. The differing effects of injuries to different parts of the brain, he based on the assumption of a varying amount of abolition to the circulation of the psychic pneuma. Soury[3] quotes him as believing that in deep comas and epilepsies the ventricles are more affected than the body of the brain, while in apoplexies the latter is more affected. In deep comas the anterior parts are more affected; in apoplexy and epilepsy the anterior and posterior are equally so.

Aretaeus, about whose personality you will remember so little is known, but who is believed to have lived and written near the time of Galen, states this question very clearly and in quite a modern sense. He says: "If, therefore, the commencement of the affection be below the head, such as the membrane of the spinal marrow, the parts which are homonymous and connected with it are paralyzed: the right on the right side and the left on the left side. But if the head be primarily affected on the right side, the left side of the body will be paralyzed; and the right, if the on the left side."[4] From this quotation it is obvious that he knew of the facts proved by Galen's experiments on the spinal cord, and one is tempted to believe that he actually knew of Galen's investigations, and that he was, therefore, either contemporaneous with Galen or wrote after him.

In explaining the crossed relationship of the brain, Aretaeus says:

> "The cause of this is the interchange in the origin of nerves, for they do not pass along on the same side, the right on the right side, until their terminations; but each of them passes over to the other side from that of its origin, decussating each other in the form of the letter X."

It will be seen that this explanation is not easily brought into accord with the statement of a homolateral effect of a lesion of the spinal cord, and is probably the expression of a current belief. Cassius Felix, who is believed to have lived during the reign of Tiberius (14-37 A. D.), and of whom both Celsus and Galen speak with approbation, gives this same explanation, and it has been thought by some that Aretaeus probably copied it from him.[5]

This idea was probably based on the crossing of the optic nerves, which is so obvious that it struck the attention of the earliest anatomists, especially those who dissected the lower forms of animals. Aretaeus does not refer to this, nor does he make any other strictly anatomical observations. Galen, on the other hand, did not regard the optic chiasm as a decussation, but a true union, where the images of binocular vision were combined before reaching the soul.[6]

The assumption of the crossing of the peripheral nerves as an explanation for the crossed effect of lesions of the brain, although based on practically no anatomical observations, was current up to the beginning of the last century.

The intellectual darkness of the following centuries obscured these clear views of Galen and Aretaeus, and during this time the conceptions regarding the nervous system appear to have been purely philosophical. In illustration of this I have taken the liberty of reproducing an interesting old diagram that Sir Victor Horsley[7] discovered in a MS. in the Bodleian Library, which was written in 1152, and is obviously based on the philosophy of Aristotle and not of Galen. It will be seen that the brain is not even indicated.

With the revival of classical learning in the Renaissance, the writings of the Greek physicians became current, particularly those of Galen, which actually dominated medical thought for many years. As anatomy began to be studied more and more from actual dissections of the human body, the views of Galen were revised, but it is interesting that the brain received but slight attention. A reference to the plates in the "Fabrica" (1543) of Vesalius (1514-1564) will show how little this part of anatomy interested him.

The tremendous intellectual activity of this period, especially along physical and mathematical lines, had its full influence on medical speculation. Descartes'[8] (1596-1650) fascinating attempt in 1662 to reduce the nervous system to an intricate "earthly machine" governed entirely by physical laws, is the most brilliant example of this.[9] He was a philosopher, and was impeded but little by accurate anatomical and physiological knowledge.

Willis (1621-1666), who worked at the same time, seems to have derived his philosophical views from Descartes, but his more accurate knowledge of anatomy and physiology of the nervous system, impeded him in his speculations. Sir Michael Foster,[10] however, has little regard for him as a philosopher, or, indeed, a man, and he thinks that even his anatomical knowledge was derived from his associate, Lower.

Willis[11] did, in fact, do much to advance our knowledge in regard to the structure of the brain. He paid much attention to the cortex of the cerebrum and cerebellum, where he thought the vital spirits were formed, to be distributed through the

[3] Le Système Nerveux Central, 1899, p. 296. Paris.

[4] The Extant Works of Aretaeus, etc., chap. VII, p. 305. The Sydenham Society, Lond., 1856.

[5] See Morgagni, Seats and Causes of Diseases, 1769, Vol. I, p. 53, sec. 19. London. Trans. by Benj. Alexander.

[6] Soury, ibid., p. 297.

[7] "The Structure and Functions of the Brain and Spinal Cord," London, 1892. Linacre Lecture. Brit. Med. Jour., 1909, July 17.

[8] See Sir Michael Foster's "Lectures on the History of Physiology," 1901, which contains a mine of information about the workers of this period.

[9] De Homine Liber. Quoted from Michael Foster.

[10] Ibid., p. 270.

[11] Practice of Physic, Treatise VI, Anatomy of the Brain, 1684, London.

medullary substance to the nerves. The corpus callosum he regarded as a sort of reservoir where the spirits from the cerebrum were collected and from which they passed out or to which they returned through the streaked bodies (corpus striatum). These latter structures he described as the beginning of the medulla, and regarded their striated appearance as indicating channels which directed the spirits. The medulla oblongata was a large and royal path, where the animal spirits, derived from their double source, the brain and cerebellum, always run abundantly. He says nothing of the crossed relationship of the cerebrum. Indeed, he seems to regard the division of the brain into two parts as being a conservative device, so that when one was injured the other could take on its function. However, in speaking of a case of hemiplegia, he explains it by the fact that one of the streaked bodies had been pressed upon, but in his description of the autopsy he neglects to mention whether this was on the side of the paralysis or on the opposite side.

"A young man of a sanguine temper, ingenious, and for the most part healthy, sitting in a chair after a large supper, and immoderate drinking of wine, was so distempered with a numbness or stupidity in his right hand, that his gloves, which he held in it, fell of themselves out of his hand; then getting up and endeavoring to walk, he felt a resolution or loosening in his thigh and leg of the same side, and a little afterwards falling into a certain hebetude or dulness of mind, and stupefaction, yet without an apoplexy; for he was still himself, answering aptly to questions asked him, though but slowly and with difficulty, and doing those things that were bid him. Presently a skillful physician being sent for, phlebotomy, vomiting, and purging were celebrated in order, cupping-glasses, scarification, ointments, frictions, and other fit administrations were carefully applied: nevertheless the palsy increased, that besides the motion of his members on the right side being taken away, he also lost the sight of that eye; yet still being stupefied and sleepy, he was compos mentis, and knew his friends, and being conscious of his infirmity, and solicitous for the recovering his health, he took all remedies were given him; but notwithstanding all this, the animal functions daily more and more languished, and at length by their consent the vital; so that about the seventh or the eighth day, from thence, falling sometimes into a delirium, and sometimes into convulsions, or other distractions of the animal spirits, his strength being at length quite lost, he yielded to death.

His head being opened, the anterior cavity of the brain was filled, partly with ichorous blood, partly concreted and in clodders or gobbets, with plenty of serum: Hence, as it is easy to conceive, from this deluge, pressing upon one of the streaked bodies, and binding up its pores and passages, the flowing of the spirits into the nervous appendix of that side was hindered, and for that reason, the resolution in the respective members was excited; and because of the optic chamber, where it is inserted into the streaked body, being also pressed together, the eye of that side lost its sight; further, because the callous body, chambering that den, was somewhat pressed by the heaped matter, from thence the hebetude and stupefaction of the chief functions of the soul were excited, yet without their subversion or inordination. By reason of the evil being fixed on the substance of the brain, and the spirits inhabiting it, these sorts of distempers do proceed, and not from the impletion of the ventricle, as appears clear enough by this instance, and by what we have elsewhere mentioned." [12]

Plate II gives his conception of the base of the brain.

[12] Ibid., p. 174.

Among the philosophical speculations of the time it is refreshing to read Stensen's [13] (1638-1686) protest, directed especially against the views of Descartes and Willis. He says: "There abounds indeed a rich plenty of men to whom everything is clear. Such, dogmatizing with the utmost confidence, make up and publish the story of the brain and the use of its several parts with the same assuredness as if they had mastered with their actual eyes the structure of so admirable a machine and penetrated into the secrets of the great artificer." He was the first to state clearly that to understand the workings of the brain, one must know the course of the fibers within its substance, for he says in another place: "If indeed the white substance, of which I am speaking be, as in most places it seems to be, wholly fibrous in nature, we must necessarily admit that the arrangements of its fibers is made according to some definite pattern on which doubtless depends the diversity of sensations and movements." [14]

Stensen's appreciation of the complexity of this pattern, and the importance of unravelling it, has been amply justified by the enormous amount of work which is even now being directed towards its elucidation.

The difficulty of this problem deterred the anatomists after Willis for many years, and no material advance, in the knowledge of the structure of the nervous system, was made for more than one hundred years, *i. e.*, until the end of the eighteenth century.

Along with the more frequent dissections of the human body, greater interest was taken in the morbid conditions found after death, and reports of autopsies began to accumulate. That the lesion in apoplexy was frequently found on the opposite side of the brain, aroused renewed interest in a number of observers.

Wepfer (1620-1695), who, in 1658,[15] first clearly pointed out the dependence of apoplexy on hemorrhage within the substance of the brain, refers to this fact when speaking of one of his own cases. He says:

"I do not indeed deny that these tumors of the ventricles may, in some measure, have conspired to the production of a hemiplegia in the left side; for I myself, with many others, have observed that one side of the brain being affected, the opposite side of the body had been seized with a palsy, but I believe that the concomitant and perhaps primary cause of the hemiplegia in this case was serum. . . . . Nor does it help forward the demonstration of this subject, that the left part of the spinal marrow was less than the right; for if it had been anything preternatural, the foot must have been incapable of motion equal with the arm." [16]

Dr. Donley, from his very thorough knowledge of Wepfer,[17]

[13] Discourse on the Anatomy of the Brain, 1669. Quoted from Foster.

[14] It is interesting to remember that Newton, in 1704, suggested that certain optical phenomena could be explained only by a partial decussation in the chiasm of the optic nerves—a deduction that had to wait many years for its confirmation.

[15] De Apoplexia. See Donley.

[16] Quoted from Morgagni, The Seats and Causes of Diseases, 1769, Vol. 1, p. 234, sec. 10.

[17] Johns Hopkins Hospital Bull., Jan., 1909, "John James Wepfer, a Renaissance Student of Apoplexy."

kindly writes me that this author, although he knew that at times the lesion was found opposite to the paralyzed side, as the case quoted above shows, still thought that, as a rule, the lesion was to be looked for on the same side, and was surprised when he found the opposite condition and usually hunted for some other cause for the paralysis.

Morgagni[18] claims for his master, Valsalva (1666-1738), the credit of having demonstrated that in hemiplegia the lesion should be looked for on the opposite side of the brain, for although this had been seen by Wepfer and many other observers, it was passed over without remark.

The importance with which Morgagni regards this may be gathered from the quaint description which he gives of a case of apoplexy occurring in a man forty years old, who was admitted to the hospital in February, 1703. Upon being brought to the hospital "the physician ordered his legs and his feet to be vehemently rubbed, spirit of salt ammoniac to be applied to his nostrils, and even some drops of it in a proper vehicle to be poured into his mouth, and the blood to be taken away from his arm, on which side he was most affected with a paralysis."[19] This treatment proved ineffectual and the patient died.

When Morgagni was about to do the autopsy, Valsalva came into the room. "Then Valsalva said to me, this apoplexy, unless my observation fails me, was brought on by blood injuring the right side of the brain."

I have been unable to discover that either Valsalva or Morgagni theorized as to the cause of the crossed relationship.

This, however, cannot be said of a fellow-countryman and contemporary of theirs, Domenico Mistichelli, professor of medicine in the University of Pisa, who wrote a book on apoplexy, which was published in Rome in 1709.[20]

In this work he speaks of the crossed relationship as a well-recognized fact, and endeavors to explain it by a new view of the anatomy of the nervous system. This author would hardly justify special attention were it not that to him is often given the credit of having first demonstrated the actual decussation of the pyramids (Gall, Neuburger, Landois, etc.).

Mistichelli's view was unique. He thought that the substance of the brain and medulla was without structure, but that the membrane (pia mater?) which surrounded them was composed of fibers which interlaced among each other in a most intricate manner, which he likened to the braid of a woman's hair. It was from this membrane that the nerves took their origin. Plate IV gives his diagram.

It will be seen that he supposed the surface of the pons to be formed of transverse fibers which passed up over the medulla, to cross and to go forward again, and so be plaited about the spinal cord. There were other longitudinal fibers which seemed to arise also from the pons, and also many others.

This book, you will remember, is on apoplexy, and in Chapter VIII he explains how a lesion on one side of the head results in a paralysis of the opposite limbs, and says, in Section II:

"To explain these facts it is necessary to remember that which was recently established by myself, namely (d) that the medulla oblongata is on the outside, interwoven with fibers, which by their criss-cross superposition, resembles a woman's braid, whence it comes that many nerves which branch out on one side, have their roots on the other. For instance, those which extend to the right arm may easily, by such an arrangement, have for roots the left fibers of the meninges, and in the same way the left may proceed from the right. This probably applies to many, if not to all, the nerves which have their origin immediately from the spinal marrow."

This he considers sufficient explanation of why, if the flow of the animal liquid be impeded on one side of the brain or medulla, the effects will be on the opposite side of the body.

The book, after all, is written for the primary purpose of advancing a new and signal cure of apoplexy, *i. e.*, the burning of the soles of the feet with a hot iron. Figure 4, Plate IV, shows the exact position where the cautery is to be applied, and it is probably to commemorate this important discovery that the frontispiece was designed.

Mistichelli's explanation differs from that given by Aretaeus only as to his fanciful anatomical ideas, and it is remarkable that he is so often spoken of as the discoverer of the decussation of the pyramids.

Of quite another character is the work of Francois Pourfour du Petit (1664-1741), who became interested in this subject while serving with the French Army in Flanders. He published his results in a little pamphlet entitled "Lettres d'un Medecin," etc., Namur, 1710, only 200 copies of which seem to have been printed, so that the book is one of the very rare medical works. I have not been able to find any copy in America, but Dr. Osler was so kind as to look at the copies in Paris and in London. He had some of the pages photographed from the London copy, and I am able to show you some slides from it. As you will see, Petit's name is not on the title page, and of the Paris copy, Dr. Osler writes that there is "no name on the title page, but in ink written 'par Francois Petit.'"

In the London copy this inscription is found:

Pourfour Du Petit—M. de Mayran gave a Eulogy of him in the Royal Academy of Science, in the year 1741. There is to be found a brief note of this book, p. 174 [translated as follows]:

"A life that was largely itinerant and little adapted to contemplation necessary for the composition of works, did not prevent M. Petit from publishing, in 1710, three dissertations in the form of letters, which were printed at Namur under the title of "Lettres d'un Medecin." He only had 200 copies printed which makes the work infinitely rare, and which necessitates our giving some idea of it. It is a little book in 4°, filled with facts, observations and experiences, etc." See the Eulogy, cited above.

This piece is marked with an asterism of approbation by M. de Haller in his Catologas Editiorum Librorum quobus Auctor, etc., subjoined to the last volume of his Elementa Physiologie, p. 223.

[18] The Seats and Causes of Diseases, 1769.

[19] Ibid., Letter III, sec. 16.

[20] Trattato Dell Apoplessia. This appears to be an extremely rare work, and the only copy of which I have been able to hear, nearer than Rome, is in the library of Harvard College. Through the courtesy of the librarian I have had an opportunity of seeing the work, and am able to show you the photographs of the title-page, frontispiece, and one of the plates. I have also photographs of certain of the pages which were most kindly made for me by Prof. Bastianelli from the copy at Rome.

Of the first "Lettre" Dr. Osler says:

"It is really a remarkable production. He first deals with the question, much discussed, as to the paralysis on the side opposite to the cerebral lesion, and refers to many old cases from Aretaeus and others. Secondly, he gives an interesting series of his own cases in which after injuries or disease (usually abscess) he found the brain lesion opposite to the affected side. Thirdly, he gives a series of "Experiences" (experiments) on dogs, in which after injury to or removal of part of the brain on one side, the paralysis was always on the opposite.[21] Lastly, he discusses the anatomy and gives a beautiful figure of the medulla and upper part of the cord, showing as clearly as Quain or Grey, the decussation of the pyramids."

Petit's description is as follows:

"Each pyramidal body divides at its inferior part into two large handfuls of fibers, more often in three and sometimes in four. Those of the right side pass to the left, and those of the left side pass to the right, reuniting with each other, as seen in *D*, in the first figure."

This, I believe, is the first actual observation of the decussation of the pyramids, and based as it is on clinical, experimental and anatomical observations, is surely a most noteworthy contribution, particularly when compared with the current knowledge of the times and such work as that of Mistichelli.

Petit's master in anatomy, Duverney (1648-1730), also describes the decussation, and says: "When the pyramidal eminences are raised, one sees, near their extremities, two or three bunches of fibers, of which some pass from the right side of the medulla to the left, and others in the reverse direction." The drawing which he gives is clearer, although somewhat more diagrammatic, than Petit's.

This plate and quotation are taken from a posthumous work,[22] which was published thirty years after his death, which occurred twenty years after the publication of Petit's "Lettres," and it seems reasonable to believe that he had incorporated his student's work, although neither he nor his editors make reference to Petit in this connection.

It is interesting that upon Duverney's retirement from the Royal Academy, Petit took his place, and was later appointed, in association with Winslow and Morand, after Duverney's death, to edit some of his notes on natural history.

That Mistichelli is so often coupled with Petit as having discovered the decussation of the pyramids, shows how little was known of the observations of either of them.

The generally accepted view at the time of Petit's work may be gathered from the description given by Thomas Gibson (1647-1722),[23] who seems to have been the most authoritative English anatomist of that time. He describes the spinal cord as being divided into two parts from its origin at the junction of the crura to its end, and says (p. 398):

"The partition is made of the pia mater and by means of it it is that the use or motion of one side only is sometimes taken away in these palsies."

This view of the almost complete separation of the two sides of the spinal cord was very firmly fixed, and Monro, 2d (1733-1817), probably in criticism of the work of Winslow, Haller and others, says:

"We have observed that the right and left sides of the spinal marrow are divided from each other by deeper fissures than have been described by many late writers, or that the right and left sides of it are less intimately connected than is commonly imagined. From attention to this circumstance, we are, in some degree, enabled to explain the cause why one side of the body is much palsied, whilst the other preserves its powers unimpaired, or to understand the cause of hemiplegia." (Chapter XI.)[24]

Monro's plate (X) of the base of the brain gives no suggestion of the decussation of the pyramids.

Sir Charles Bell himself, in his early dissections of the spinal cord, was governed by the same belief, and traced the anterior columns directly into the same side of the cerebrum.

Santorini (1681-1737) is also credited with having demonstrated the decussation of the pyramids.[25] He refers to Mistichelli's observations, and says on account of their obscurity that they have been doubted by many, but that he (Santorini), himself, has shown these crossed connections so completely that no one can longer doubt. He describes them as occurring in three different places, but his description is difficult to understand, and the copy which I had the opportunity of examining contained no plates.[26]

Winslow (1669-1760) also, and a number of other authors, described more or less intimate connections between these two sides, and he believed that he had confirmed Petit's observation, for after speaking of the spinal cord as taking its origin from the pyramids and olives, structures, the names of which he reverses, and describing the fissures of the cord, says[27] (p. 110):

"When we separate these ridges with the fingers we observe a crucial intertexture of several small medullary cords which go

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[21] Neuburger, Die Historische Entwicklung der Experimentellen Gehirn und Ruckenmarksphysiologie vor Flourens, p. 52, et seq., speaks somewhat more in detail of the experiments, and says that Petit usually trephined over the middle of the parietal lobe, and inserted a scalpel in various tracts and varying depths. As a result of these procedures, he found paralysis always of the opposite extremity, but he noticed that this paralysis was only complete when the corpus striatum was injured, for if the injury was confined to the cortex there was no real paralysis but simply a weakness of the opposite side.

[22] Oeuvres Anat., 1761, Vol. 1.

[23] Anatomy of Human Bodies Epitomized, 1703, London, VI Ed.

[24] Observations on the Structure and Functions of the Nervous System, 1783, Edin.

[25] Observ. Anat. Lug. Bat., 1739. Cap. 3, sec. 12, p. 61.

[26] Yelloly (cf. p. 24) says: "Santorini referred the place of decussation to the tuberculum annulare, as well as to the medulla oblongata; but was induced to consider it as taking place in the latter, from the circumstance of the existence of fibers, which appeared to him to decussate. We are informed, however, by Vicq d'Azyr, that M. Girardi, the editor of the posthumous works of Santorini, examined 34 brains in order to ascertain whether the decussation mentioned by him takes place, but was not able to convince himself of the fact. Vicq d'Azyr himself considers the fibers as nothing more than commissures, and not at all connected with the phenomenon in question."

[27] An Anatomical Exposition of the Structure of the Human Body. Trans. by G. Douglas, 1756, Ed. IV, London.

obliquely from the substance of one lateral portion into the substance of the other. M. Petit, Member of the Royal Academy of Science, and Doctor of Physick, is the author of the discovery by which we are able to explain several phenomena both in physiology and pathology."

Winslow does not mention just where he sees these crossing fibers, nor do any of his plates indicate that he actually saw the decussation of the pyramids.

Haller (1708-1777), to whom we owe so much in regard to the physiology of the nerves and muscles, gives a very similar description.[28] In speaking of the fissures of the cord he says: "Each of these sulci is continued down along the medulla spinalis, the anterior most evidently; the posterior less so. In the former transverse fibers are detected from the right to the left, both in the medulla oblongata and spinalis" (p. 166, 1st Am. Ed.). These transverse fibers he regards as analogous to other bands which connect the two sides of the nervous system, and adds: "And most of them join the right and left parts together, as the anterior commissure and the two posterior, the corpus callosum, the striæ between the process from the cerebellum to the testes and the medullary cross-bars, in the bottom of the third ventricle, and in the medulla oblongata and spinalis" (p. 185). This, he thinks, explains the crossed paralysis, but he also thinks, as did Willis, that it is a contrivance by which each side of the body is supplied with nervous energy from both sides of the brain, so that an injury to the brain does not always paralyze.

Boruttau[29] says that Haller accepted with enthusiasm Petit's view, but gives no exact reference, and this, I think, can hardly be possible from the quotation given above.

Vieq d'Azyr (1748-1794) seems also to have regarded these connections as commissures.

Many more citations could, without doubt, be given, but these are sufficient to show that du Petit's discovery had either been overlooked or misunderstood, and that the decussation was practically unknown when Gall, the phrenologist, again called attention to it.

Francis Joseph Gall[30] (1758-1828), as an anatomist of the nervous system, appears to me to be far ahead of his generation. He believed that the white or fibrinous matter of the central nervous system was directly related to the gray or cineritious substance, and that this latter in some way formed the former. All the nerves, both cranial and spinal, he believed to arise from the medulla and spinal cord. The brain he regarded as an outgrowth from the cord, and as being composed of excurrent and recurrent nerves, or, as we would say, afferent and efferent. The cortex was a peripheral mass of gray matter, or ganglion, and in some way gave rise to the recurrent nerves. In tracing the pyramidal fibers, he showed that they passed through masses of gray matter, from which they seemed to receive fibers, and he pictures very beautifully their decussation at the lower part of the medulla oblongata.[31]

Although Gall had been demonstrating the brain in the capitols of Europe for a number of years, it was not until 1810 that he, in association with Spurzheim, published the first volume of his work, but a year previous the commission appointed by the Class of Mathematical and Physical Sciences of the National Institute of Paris, reported on a memoir[32] which these authors had presented.

Gall and Spurzheim had a thorough knowledge of the literature and refer to Petit's work, but give Mistichelli the credit of the first discovery, and make many other references which were generally copied by subsequent writers.

In speaking of Gall's demonstration of the decussation of the pyramids the commission says (p. 57):

"How has it happened that a point of structure so evident, adopted by Winslow, Lieutard, Portal, distinctly described and plainly delineated by Santorini, should have been doubted by the great Haller, recently denied by very skillful men, and confounded by others, among whom may be reckoned Vicq d'Azyr himself, with that of the transverse fibers which unite, in their whole length, the lateral parts of the medulla oblongata?"

The opposition which was aroused by Gall's peculiar phrenological views, and his somewhat startling method of their exploitation, probably accounts for the tardy acceptation of his anatomical discoveries.

An excellent illustration of the attitude of the best medical thought at the beginning of the last century, in regard to the crossed relationship of the brain, can be gathered from a paper read in 1808, by John Yelloly, concerning a patient who died with a tumor involving the lateral side of the pons, and which caused paralysis of the VI and VII nerves on that side, together with the opposite arm and leg.[33]

In relation to this case, Yelloly was particularly interested in the question of the conduction of the nervous impulses in the spinal cord and says:

"I shall consider whether there is reason to suppose that nervous energy, in whatever that may consist, is in its progress to the spinal nerves confined to the particular side from which these nerves proceed; whether it is subject to any decussation; or whether it is equally dependent, for its propagation, on the whole spinal column."

In the body of his paper he does not even refer to the decussation of the pyramids, but speaks of the older views of Galen, Aretaeus and some of the modern writers who accepted them. He got his friend, Sir Ashley Cooper, to make hemi-sections of the spinal cord to confirm Galen. In a footnote he refers to the report of the commission on Gall's work, but points out

[28] Physiology, etc., 1754, London. Also first American edition, Troy, 1803.

[29] Neuburger and Pagel: Handbuch der Geschichte der Medizin, 1901-3, Vol. II, p. 355.

[30] Renewed interest is being taken in this remarkable and picturesque man. The fact of the "Gall Society" is an evidence of this. See "The Unknown Life and Works of Dr. Francis Joseph Gall" by Bernard Hollander, being an inaugural address delivered before the "Gall Society" on May 15, 1909. Published by Siegle, Hill & Co., London.

[31] Anatomie et Physiologie du Système Nerveux en Général et du Cerveau en Particulier, etc., Paris, 1810.

[32] Report by Tenon, Portal, Sabatier, Pinel and Cuvier. Trans. Edin. Med. & Surg. Journ., 1809, Vol. V, p. 36.

[33] "A Case of Tumor of the Brain," Medico-Chirurgical Trans., 1809, Vol. 1, p. 181.

that even if the decussation of the pyramids were true, it could hardly explain the paralysis of the face on the same side as the limbs, as this occurs after the giving off of the facial nerves, and that the cerebral influence must cross the middle line somewhere above the origin of the facial nerve.

Even the mere fact of the crossed relationship was doubted, and John Cheyne (1777-1836), in his interesting monograph on apoplexy,[34] writes concerning this point that he is only justified in saying that his dissections tend to confirm the observation that the blood is generally extravasated in the hemisphere opposite the side of the body which is paralyzed, and Craigie (1793-1866), as late as 1850, wrote: "Palsy of the opposite side, though frequent, is not an invariable result of injury of the brain."[35]

However, in 1853, Romberg (1795-1873), in speaking of cerebral localization, says: "The fact that is most positively established, and is scarcely threatened by a single exception, is the law of crucial conduction (p. 416)."[36]

As has already been pointed out, Gall's views made but little impression on anatomists in general. Sir Charles Bell (1775-1842), in the development of his idea of a new anatomy of the brain, appears to have entirely disregarded them, although he can hardly have been ignorant of them.[37]

You will remember that he believed that the nerves differed in function, depending upon the part of the brain to which they went, or from which they arose, and his particular interest was in elucidating this point by dissection. He early got the notion[38] that the posterior roots differ from the anterior in function; that the anterior were motor and that the posterior were sensory. He traced the anterior roots from the anterior columns of the spinal cord, and traced these columns up through the medulla, pons and into the cerebrum, at first taking no notice of the decussation, but later, in a paper read before the Royal Society in 1834, he gives a very beautiful drawing.

In this paper, while speaking of the functions of the different parts of the central nervous system, he says:

"It will not be denied that the most unequivocal proof of the little success that has attended the efforts made to improve this part of physiology, is the failure of all attempts to explain the phenomena which attend injury of the brain; it is neither said why, in disease of the brain, sensation and motion should be lost together, nor why one faculty should sometimes be imperfect and the other entire. There is no satisfactory reason given for the most common occurrence in practice, the loss of motion and sensation on the side of the body opposite to that side of the brain which has received the injury; nor has the condition of the face, as associated with that of the body, been accounted for. When circumstances so remarkable present themselves daily, consequent upon accident or disease affecting the brain, without our teachers succeeding in offering a satisfactory reason for them, it is obvious that we are in a state of profound ignorance of the most interesting functions of the animal body, notwithstanding the innumerable experiments which have been made upon the brains of animals."

He thought that dissection as he practised it was the only thing that could unravel this point, and says:

"On this plan I now propose to demonstrate that sensibility and motion belong to the cerebrum—that these two columns descend from each hemisphere—that one of these, the anterior, gives origin to the anterior roots of the spinal nerves, and is dedicated to voluntary motion—and that the other (which from its internal position is less known) gives origin to the posterior roots of the spinal nerves, and to the sensitive root of the fifth nerve, and is the column for sensation.

"Further, I propose to show that the columns of motion which come from different sides of the cerebrum join and decussate in the medulla oblongata—that the columns of sensation also join and decussate in the medulla oblongata. Finally, that these anterior and posterior columns bear, in every particular, a very close resemblance to one another—that is to say, the sensorial expansions of both are widely extended in the hemispheres: they pass through similar bodies towards the base of the brain, and thus concentrate and decussate in the same manner, thus agreeing in every respect except in the nervous filaments to which they give origin."

He at first traced the posterior roots into the posterior columns, and these he traced into the cerebellum, and his first idea was that this was the sensory part of the brain. This view, however, was so contradictory to his general view, that motion and sensation were always together, that he later traced the posterior roots into the lateral columns (Plate XIII, Figs. 2 and 3, Fig. 4, *c*) and these he dissected up to the medulla, discovered that they decussated (Plate XIV, Fig. 2, *c;* Plate XV, Fig. 5, *d*) joined in a single bundle, then separated (Plate XV, Fig. 5, *ee;* Fig. 6, *aa*) proceeded to the cerebrum, passing through or ending in the optic thalamus, whereas the motor tracts he traced to the corpus striatum and beyond.

One is struck by the ingenuity with which Sir Charles Bell traced his tracts, and although his dissections were in part factitious, still that he did actually announce the fillet as the sensory tract of the brain is certainly astounding. Plate XVI

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[34] Cases of Apoplexy and Lethargy, 1812, London.

[35] Elements of General and Pathological Anatomy, 1851, 2d ed., p. 310. Philadelphia.

[36] Diseases of the Nervous System, 1853, Vol. II. New Sydenham Soc.

[37] The only reference to Gall that I have found is in his paper, "On the Nerves of the Orbit," read before the Royal Society, June, 1823.

He says: "The most extravagant departure from all the legitimate modes of reasoning, although still under the color of anatomical investigation, is the system of Dr. Gall. It is sufficient to say, that without comprehending the grand divisions of the nervous system, without a notion of the distinct properties of the individual nerves, or having made any distinction of the columns of the spinal marrow, without even having ascertained the difference of cerebrum and cerebellum, Gall proceeded to describe the brain as composed of many particular and independent organs, and to assign to each the residence of some special faculty.

"When the popularity of these doctrines is considered, it may easily be conceived how difficult it has been, during their successive importations, to keep my pupils to the examples of our own great countrymen. Surely it is time that the schools of this kingdom should be distinguished from those of other countries. Let us continue to build that structure which has been commenced in the labours of the Monros and Hunters, and which the undeserved popularity of the continental system has interrupted."

[38] "Idea of a New Anatomy of the Brain." Printed for private circulation, probably in 1811.

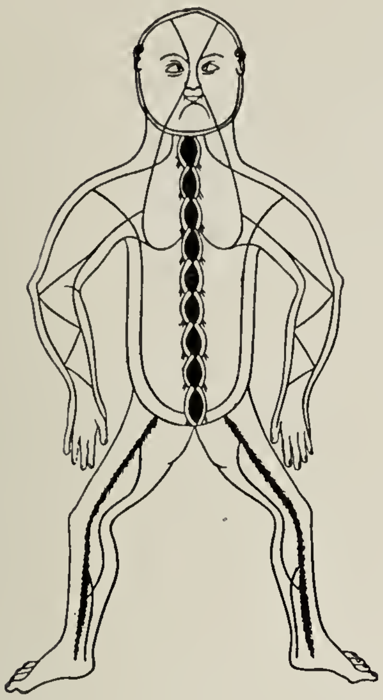


Plate I.

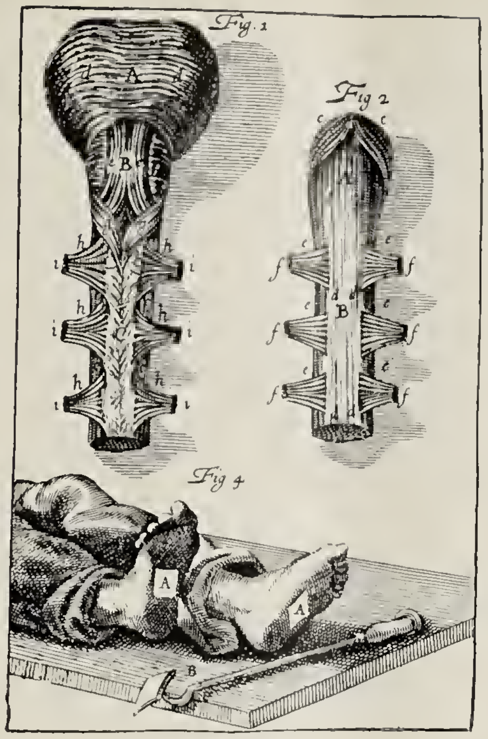


Plate IV.

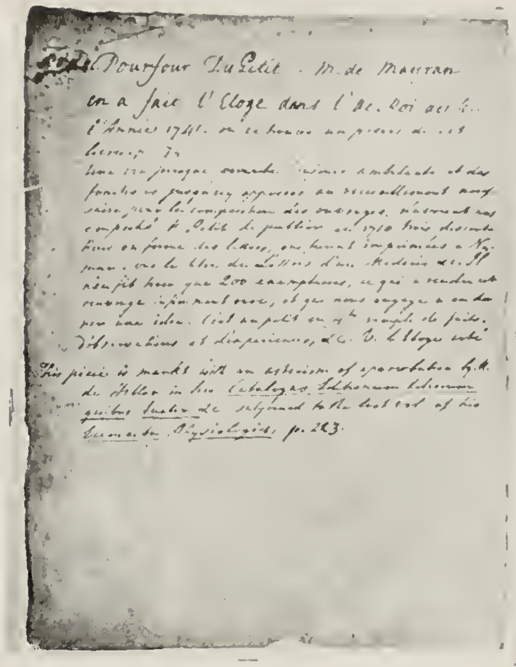

Pourfour Du Petit . M. de Mairan en a fait l'Eloge dans l'Ac. Roi des Sc. l'Année 1741.

Plate VII.

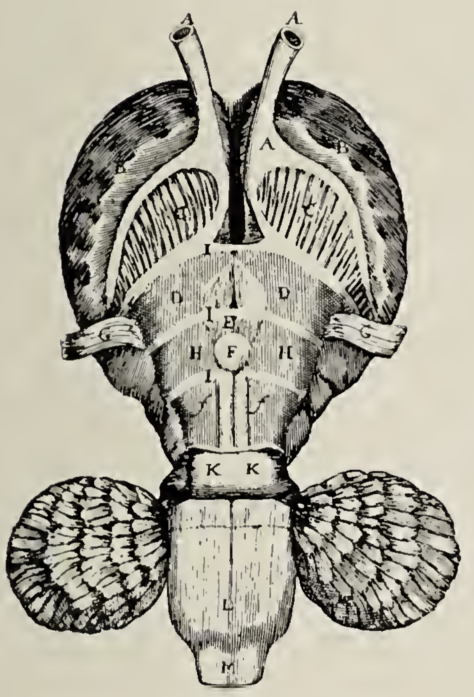


Plate II.

Plate V.

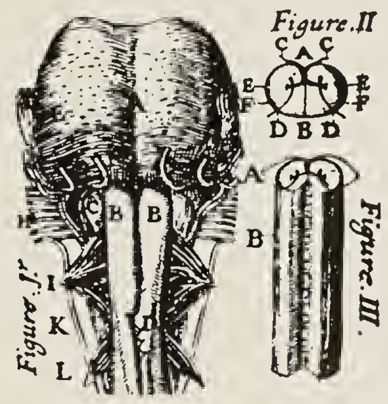
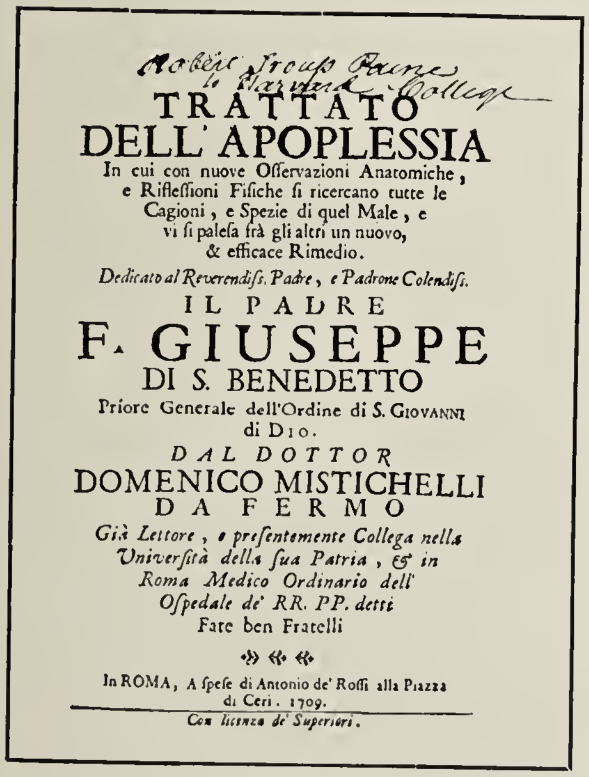

Châque Corps Piramidal se divise à sa partie inferieure en deux grosses Manipules de Fibres, le plus souvent en trois & quelquefois en quatre. Celles du côté droit passent au côté gauche, & celles du côté gauche passent au côté droit, en s'engageant les unes entre les autres, comme on le voit en D dans la premiere Figure.

FIGURE II.

Elle répresente la Moelle de l'Epine coupée en travers.

Plate VIII.


TRATTATO DELL' APOPLESSIA

In cui con nuove Osservazioni Anatomiche, e Riflessioni Fisiche si ricercano tutte le Cagioni, e Spezie di quel Male, e vi si palesa frà gli altri un nuovo, & efficace Rimedio.

Dedicato al Reverendiss. Padre, e Padrone Colendiss.

IL PADRE

F. GIUSEPPE

DI S. BENEDETTO

Priore Generale dell'Ordine di S. GIOVANNI di DIO.

DAL DOTTOR

DOMENICO MISTICHELLI

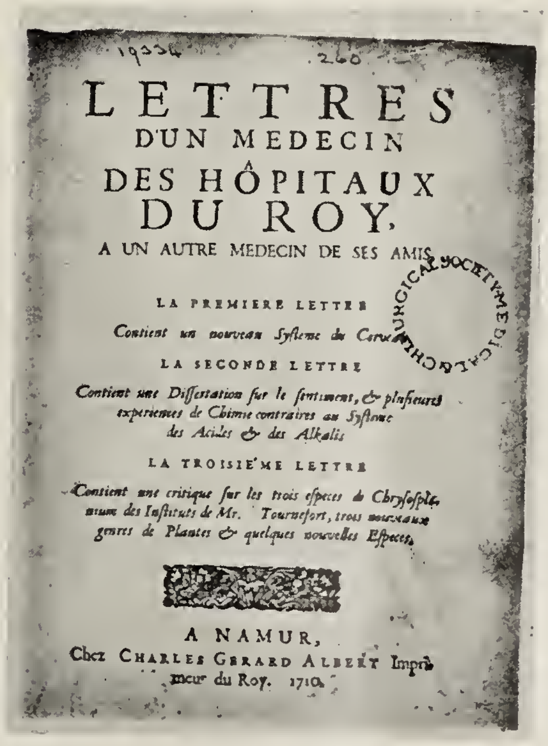
DA FERMO

Già Lettore, e presentemente Collega nella Università della sua Patria, & in Roma Medico Ordinario dell' Ospedale de' RR. PP. detti Fate ben Fratelli

In ROMA, A spese di Antonio de' Rossi alla Piazza di Ceri. 1709.

Con licenza de' Superiori.

Plate III.


LETTRES

D'UN MEDECIN

DES HÔPITAUX

DU ROY,

A UN AUTRE MEDECIN DE SES AMIS.

LA PREMIERE LETTRE

Contient un nouveau Systême du Cerveau

LA SECONDE LETTRE

Contient une Dissertation sur le sentiment, & plusieurs experiences de Chimie contraires au Systême des Acides & des Alkalis

LA TROISIE'ME LETTRE

Contient une critique sur les trois especes de Chrysosple-nium des Instituts de Mr. Tournefort, trois nouveaux genres de Plantes & quelques nouvelles Especes.

A NAMUR,

Chez CHARLES GERARD ALBERT Imprimeur du Roy. 1710.

Plate VI.

Plate IX.

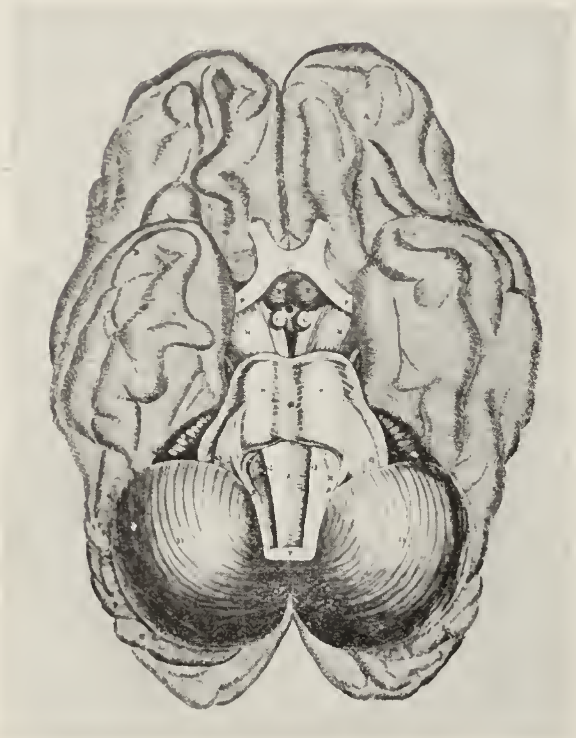


Plate X.

Plate XII.

Plate XIV.

Plate XI.

Plate XIII.

Plate XVI.

Plate XV.

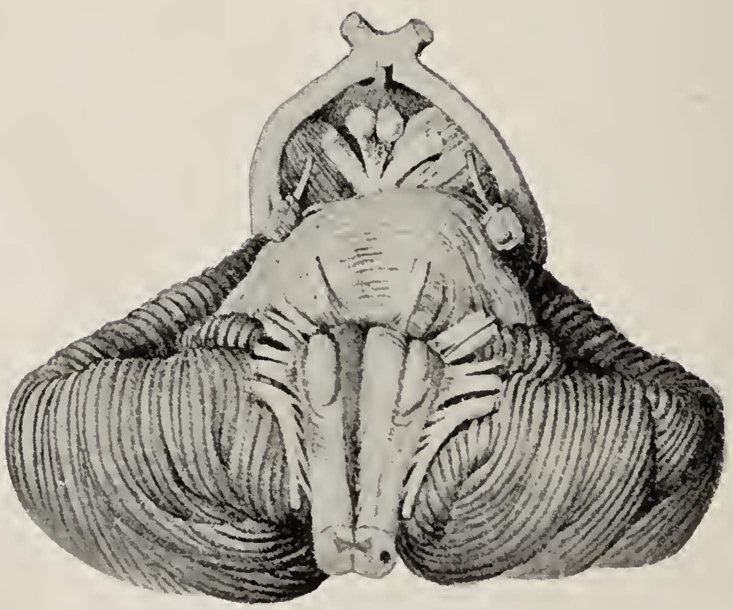


Plate XVII.

gives a lateral view of these two tracts—the motor, *c;* the sensory, *e.*

Sir Charles Bell speaks with some derision of those physiologists who considered that finding a few fibers that decussated at the bottom of the pyramids explained satisfactorily the loss of sensation and motion, for he points out that they did not know the functions of these tracts, and did not appreciate that they were entirely motor, and so could not explain the loss of sensation, and that it was not until his demonstration of the decussation of the sensory fibers in the medulla that a real understanding could have been had. He entirely overlooked Galen's experiments on hemi-sections of the cord, and their confirmation by Sir Ashley Cooper—an illustration of how he was misled by his dependence on anatomical investigations, rather than on physiological experiments.

One would suppose that after its rediscovery by Gall, and the beautiful dissections of Sir Charles Bell, that the decussation of the pyramids would have been generally accepted. This, however, was not the case. Craigie,[39] in the 1851 edition of his work, denies it absolutely. He was familiar with the literature, and seems to have even confirmed the references in the original. He contended that the only decussation that had been proved was that of the restiform processes, and says: "Neither the pyramidal nor the olivary, nor even the whole of the restiform bodies partake of it" (Amer. Ed., p. 260).

This uncertainty in regard to what to us seems such a simple obvious fact, is not to be wondered at when we remember that for its satisfactory explanation there had to be an accurate knowledge of at least some of the tracts within the central nervous system, and of how far from complete our present knowledge is in regard to any one of them.

It must be remembered that the methods were not such that were adapted to unravel the intricate course of fibers within the nervous system, that although assumed by many authors, it had not been proved that the nerves arose from cellular elements in the gray matter.

Albert von Kolliker (1817-1905), even as late as 1850, assumed that practically all the nerves arose from the brain, and that the spinal cord was a mere cable.[40]

[39] Elements of General and Pathological Anatomy. First ed. published 1828. Amer. reprint, 1851. Philadelphia.

[40] Mikroskopische Anatomie oder Gewebelehre des Menschen, 1850. Leipzig.

As the histological methods became more developed the origin of the nerve-fibers from the nerve-cells was demonstrated. Schroeder van der Kolk (1797-1862) claims to have been the first to have demonstrated this fact clearly. However this may be, it was about this time, and due to his work and that of other investigators, Lockhart Clarke among others, that this was thoroughly established. The experiments of Van Deen, Brown-Sequard, Stilling and many others, had determined much in regard to the physiology of the nervous system, and had also given rise to various theories as to the paths of conduction, etc., but it was not until the effects of secondary degeneration were studied, first by Turck,[41] and then by Bouchard, Charcot, etc., that our modern conception of the tracts within the nervous system began to be evolved.

Cruveilhier[42] had first called attention to the fact that lesions of the brain affect the nutrition or size of the brain stem, although he was unable to see that they had any effect on the spinal cord. This he thought likely. It is interesting to remember that Wepfer, in a case of lesion of the brain, noted that the contralateral side of the cord was smaller, but he did not bring these two facts into relation; indeed, he thought there was no relation (quoted from Morgagni; referred to above).

Turck described with fair accuracy the secondary degenerations which followed lesions in various parts of the central nervous system. He confirmed the decussation of the pyramidal tracts, and he recognized the existence of a direct tract which ran down the ventral columns of the cord without decussation. His plates were very crude.

Bouchard[43] continued and extended this work, and gave much more accurate pictures. I show the diagram.

Flechsig's[44] study of the tracts of the central nervous system by the method of the time of their myelinization, added much to our knowledge of the exact course of the various tracts, and especially to our knowledge of the decussation of the pyramids.

With these methods, and with others that have been advanced since, modern investigation is still concerned, and I shall not presume to speak of them before this audience.

[41] Ztschr. d. k. k. Gesellsch. d. Aerzte zu Wien (1852) II, 511: (1853), II, 289.

[42] Anatomie pathologique, liv. XXXII.

[43] Archives gen. de méd., 1866.

[44] Die Leitungsbahnen in Gehirn und Ruckenmark des Menschen, 1876. Leipzig.

AN HISTORICAL SKETCH OF BLOOD-LETTING.*

By Joseph T. Smith, Sr., M. D., Baltimore, Md.

The practice of blood-letting is one of the oldest; it has been used to combat disease for more than two thousand years, and the earliest medical writers make mention of it, but its origin is unknown.

Hippocrates drew blood from the arm, feet, legs, forehead and from under the tongue, employing the measure as a simple evacuant, as a derivative for the purpose of giving the blood and animal spirits free movement in cases of apoplexy and palsy because stagnation was believed to exist and to cool the body. He recommended its use in violent and acute diseases in the strong, particularly those in middle life, but thought it harmful in the very young, the old and feeble. If the occa-

* Read before The Johns Hopkins Hospital Historical Club, February 14, 1910.

sion seemed to require it, he did not hesitate to take enough blood to produce complete syncope, taking as his guide the color of the flowing blood; if this changed from red to dark or from dark to red, the flow was stopped. His bleedings seem to have been done only for the relief of pain, a vein being opened as near as possible to the part affected, no matter how high, or ardent as the expression was, the fever ran, blood was not drawn unless inflammation was present. It is of interest to note that Hippocrates makes no mention in his writings of the amount of blood necessary to be drawn. He does not appear to have practiced arteriotomy nor to have known the use of leeches.

Erasistratus and his followers caused the practice to fall into disuse; they thought the loss of blood, in addition to abstinence, would weaken the patient too much, that it was often difficult to discover the proper vein to open and there was danger of opening an artery; they furthermore believed that it was not possible to know what quantity of blood to take—if too little, good results would not follow, if too much, the patient might die and lastly they feared lest the escape of the blood might be followed by that of the animal spirits.

Asclepiades brought blood-letting to the front. He believed that all phenomena of living bodies were dependent upon the motion of corpuscular atoms through corresponding pores and that disease consisted in a want of correspondence between those corpuscles and pores; hence he used scarification with cupping to open the pores. Pain seems to have been his guide in the use of the lancet; in cases of inflammation without pain no blood was taken; thus pleurisy called for blood-letting, not pneumonia.

Aretaeus and Celsus were very favorable to the practice; the former used small and frequent bleedings rather than one large one. He seems to have been among the first to draw blood from the arteries, and he bled to produce relaxation of the solids in order to facilitate the passage of urinary calculi, etc. Celsus made a critical and extensive study of the subject and was bold in the practice in that he did not consider the age, only the strength of his patient, and he determined the strength by the quantity and quality of the blood; he would not bleed before the second day, as the humors were still crude and not ripe for evacuation, nor after the fourth, as by that time the bad humors would have been spontaneously dissipated or have made their full impression upon the system; he confirmed the observation of Hippocrates, that a change in the color of the flowing blood meant harm.

Phlebotomy seems to have held its own down to the time of the vain but meritorious Galen, who appears to have been the first to note the amount of blood which should be drawn, the largest quantity he speaks of being one pound and a half and the smallest seven ounces; he bled when the fever was lowest and on the affected side.

Avicenna and the Arabian physicians followed the Greeks. They took issue with Hippocrates, as they believed, in cases of pleurisy that blood should be drawn from the side opposite the disease, a trivial matter from our viewpoint, but at the time it caused many great and earnest discussions in the schools of physic. Volumes were written and published in support of the two sides and the dispute became so great that the University of Salamanca issued a decree that no one should dare to let blood from the side affected and to add authority to the decree, endeavored to procure an edict from Charles the Fifth alleging that the contrary practice was as prejudicial to the community as Luther's heresy itself.

Among the Egyptian physicians blood-letting was practiced to a very great extent, both arteries and veins being opened. They had no dread of opening an artery, although they exercised great care. A ligature was applied and when the artery was distended, the smallest incision possible to admit the flow of blood was made with a very sharp instrument; after sufficient blood was taken, lint was placed over the wound, on this a coin and the whole was firmly bound down for three days.

The history of blood-letting is a long and interesting one; we learn from it that the practice has failed to secure a firm and well-defined position. In 1830, in the June number of the "Baltimore Monthly Journal," three pages are devoted to a selected review of a proposed "plan for the investigation of the due administration of blood-letting, by Marshall Hall, M. D." The review says: "No remedy is now more general —not even calomel or blue pill—and this fact may assure us that no remedy is more abused."

A review of blood-letting during the ten years, 1830-1840, when it was extensively practiced and at a time when medical practice was to a large extent freed from the myths and legends of the ancients, will give us the best insight into the subject, and for that purpose we have made free use of the books before us: "Lectures on Blood-letting," by Henry Clutterbuck, M. D.; "The Blood," by F. Magendie, M. D.; "Curiosities of Medical Experience," by J. G. Millenmen, M. D.; "The Baltimore Monthly Journal of Medicine and Surgery," 1830; and "A Treatise on the Blood, Inflammation and Gunshot Wounds," by John Hunter, with notes by James F. Palmer.

It may be of interest to note first the earlier opinions held in regard to the blood and circulation. One of the controversies was in regard to the life characters of the blood, was this fluid in whole or in part endowed with life or was it merely a dead fluid material from which the living matter was formed? John Hunter seems to have been the first to establish a rational system and a reference to his beliefs and opinions may not be out of place. He thought that life existed in every part of the body and studied the blood with that understanding. He says: "The difficulty of conceiving that blood is endowed with life while circulating arises merely from its being a fluid and the mind's not being accustomed to a living fluid."[1] Hunter thought coagulation a life action, as in union by the first intention particle unites with particle by cohesive attraction, for he says: "Union by the first intention is no more than the living parts separated—forming a reciprocal attraction of cohesion with the intermediate coagulum."[2]

[1] J. G. Millenmen: Curiosities of Medical Experience, p. 216.
[2] J. Hunter: A Treatise on the Blood, etc., p. 43.

The fluidity of the blood in the vessels was attributed to some unknown inherent principle. This coagulating lymph he considered the essential part of the blood, because it is to be found in all animals, and because, under certain circumstances, it is capable of "undergoing spontaneous changes, which are necessary to the growth, continuance and preservation of the animal."[3] The serum, he believed, common to the blood of all animals, but was most abundant in those which had red blood; it was lighter than other parts of the blood and the stronger the coagulation of the lymph the more serum could be obtained; it might be found without being separated from coagulating lymph, as in dropsy, and the fluid in which the fetus swims. The function of the serum he considered was to keep the red corpuscles suspended and prevent their solution; it also served to suspend or dissolve coloring matters and foreign substances, as is seen when the coloring matter of the bile is found in the blood in cases of jaundice or after the administration of rhubarb. He seems to have attached much importance to a "wheyish" appearance in the serum, which he observed most frequently "in the blood of breeding women" and which upon setting "often throws up a white scum like cream." In viewing this cream under the microscope it was "plainly globular." "The globules of white serum differ from the red globules in color, specific gravity, size and in not dissolving in water."[4] The red part of the blood he thought the least important; the red globules, he believed, had a determined shape and size and that they were regular so that two could not unite as could two drops of oil. He did not seem able to account for their peculiar properties, as he says: "What this property in the red part is I do not know, for it has something like the nature of a solid body; yet the particles seem not to have the properties of a solid, for to the touch they yield no feeling of solidity. When circulating in the vessels they may be seen to assume elliptical forms, adapting themselves to the size of the vessels; they must, therefore, be a fluid with an attraction to themselves while in the serum which forms them into round globules, yet without the power of uniting with one another, which may arise from their central attraction extending no further than own circumference."[5] As to their use, he says: "Whatever may be their utility in the machine, the red globules certainly are not of such universal use as the coagulating lymph. . . . . Their use would seem to be connected with strength."[6] The red globules, he thinks, give the color to the blood and the influence of air upon that color greatly interested him. "Many substances," he says, "change the color of the blood . . . . as the air produces this effect in the living body and as we find that without air the animal dies, great stress has been laid on this change of color, whereas it should only be considered as a sign that the blood has been in contact with the air, but not that it must be fit for the purpose of circulation. . . . . Most probably the effect of air upon the blood is greatest on the coagulating lymph; and this conjecture is rendered more likely when we consider that in animals which have no red globules of any kind respiration is as essential as in any other."[7] The blood, then, as Hunter knew it, consisted of three parts, the serum, the lightest; the lymph, or solid portion; and the red globules, the heaviest. A word in regard to his views of inflammation. The "act of inflammation," as he calls it, is attributed to increased action of the vessels, chiefly, if not altogether, in the smaller ones; these, when the stimulus causing the trouble is applied, are distended beyond their normal limits and size, this being an active dilatation, the blood has no change impressed upon it in passing through from the arteries to the veins; the increased redness was attributed not only to the fact that more blood reached the part by means of the dilated old vessels, but that new vessels were formed in the extravasated lymph. The swelling, he thought was due to extravasated lymph, the serum not being thrown out, as in dropsy, but squeezed out from the coagulating lymph. The pain was thought to be caused by increased nerve action brought about by the enlarged blood-vessels and the thrown-out lymph, the nerves themselves not being inflamed. Heat was regarded as a sign usually of strength and power of constitution and that it meant positive action, but the actual increase of the heat in inflammation he does not think as great as it seems to the senses; he says: "As inflammation is the principal instance capable of producing local heat I have taken the opportunity of examining inflammations . . . . I have also made several experiments . . . . and cannot say that I ever saw . . . . a case where the heat was really so much increased as it appeared to be to the sensations."[8] Magendie, in his lectures on the blood, delivered in 1837-1838, follows much in the line of Hunter's teachings; he speaks of fibrin and discusses the phenomena of coagulation. The red corpuscles he thought lost the ability to pass through the capillaries if modified in form or size. He treats in detail of a property of the blood, he terms it "viscousness," because by it the fluid is able to pass through the minutest capillaries which otherwise would be impossible. He uses as proof the experiment with water, which cannot be forced through the very minute vessels unless gum, gelatine or albumen are added "when the attempt at injection becomes successful immediately." He strongly disapproves of bleeding from points of election, the matter which gave rise to such a serious discussion as noted in the history. He says: "No one would have had hardihood enough to deny the excellent effects ascribed to bleeding practiced in those points of election, as they are called, while the theory which led to their adoption seemed so logically established. I confess I myself formerly shared in the belief professed by a majority of medical men on the point; but if you reflect on the matter, you will see that such a notion is utterly devoid of foundation. If the circulation were formed of a series of rings, mutually independent of each other, we might rationally open one vessel rather than another, according to the site of the disorder we had to com-

[3] Idem: p. 44.
[4] Idem: p. 62.
[5] Idem: p. 65.
[6] Idem: p. 72.
[7] Idem: p. 79.
[8] Idem: p. 323.

bat; but the chain formed by the arterial tubes is perfectly continuous throughout the frame. The pressure cannot diminish at one point without doing so to the same extent in every other. Whether you bleed from the temporal or the tibial artery, the effects will be mechanically the same in respect of the circulation of the brain. The preference given the former of these vessels is justified by its superficial position which renders it easily accessible; but as regards the therapeutical influence of its division, it can lay claim to no real superiority. If you represent by five the diminution of pressure in the temporal, you must represent by five also that in the tibial artery." [9] That his belief was not universal is seen where he says: "Further, it is a common inquiry, whether in cases of pneumonia of the right lung we should bleed at the right side; and in cases where the left organ is affected, at the left? Opinions are still divided on this point. . . . . But there is another method of blood-letting which is reserved for great and important occasions . . . . I mean cross-bleeding. . . . . Suppose a case in which a variety of therapeutical measures have proved unavailing. . . . . A consultation of medical celebrities is, of course, held and upon what do you suppose the deliberations sometimes turn? Upon the propriety of opening a vein in the right arm, at the same time as another in the left foot! Is there, I would ask, such a very great difference between the employment of amulets . . . . and the confidence attributed to bleedings the jets of which cross each other in the form of an X." [10]

The blood during the period, then, of ten years was regarded as a living fluid, composed of serum and red corpuscles; upon withdrawal from its vessels coagulation took place by the organization of fibrin, which formed the clot, this clot enmeshing the corpuscles and squeezing out the serum; the circulation of the blood in the minutest capillaries was made possible by the viscousness of that fluid and the fact that the corpuscles were able to conform themselves to the shape and size of the tubes, and lastly, although the belief was not universal, that the point of election was only one of convenience.

The changes induced in the healthy body by the withdrawal of blood were classified as primary and secondary, importance being attached not only to the quantity but to the rapidity of its withdrawal, six or eight ounces taken slowly producing no very striking effects, while 12 or 20 ounces taken rapidly would cause a feeling of languor, a weakening of the pulse, a pale, cold skin with cold sweat ending in syncope. Fainting was regarded as a very important indication, and Dr. Hall, in the review noted above, devotes a great deal of space to a discussion of the subject, as did most of the writers of that day. The review says: "It is certain that if several persons be bled deliquium in the erect posture, they being of apparently similar strength but affected with dissimilar diseases, they will be found to have lost very different quantities of blood before fainting is induced. Dr. Hall has known a patient, not apparently very feeble, to faint on losing four ounces of blood, while he has seen other patients bear the loss of 50, 60 or even 70 ounces of blood without syncope. How is this to be explained? Its rationale is to be found, I believe, in connection with an equally interesting fact, that different diseases induce" (in) "the constitution different powers or susceptibilities in regard to the effects of loss of blood. Each disease appears, indeed, to possess its own peculiar and intrinsic virtue in this respect. This is determined by placing the patient perfectly erect and bleeding to incipient syncope; the quantity of blood which flows is the measure of the protective influence of the disease in one class of cases, and of its influence in superintending a susceptibility to the effects of blood in the other.

"An interesting scale of diseases may be formed representing these properties. It would begin with congestion of the head or a tendency to apoplexy; inflammation of the serous membranes and of the parenchymatous substance of various organs would follow; and lastly, inflammation of the mucous membranes. This part of the scale would be divided from the next by the condition of the system in health. Below this would be arranged fever, the effects of intestinal irritation, some cases of delirium, reaction from loss of blood and disorders of the same class with hysteria, dyspepsia, chlorosis and cholera morbus." Again: "In inflammation much blood should be taken and much blood will flow before deliquium is induced; in irritation little blood should be drawn; and there is early syncope from blood-letting" (Balt. Month. J. M. & S., p. 208, etc.).

The immediate effects of blood-letting were believed to be caused by the rapidity of the withdrawal and the after effects by the quantity withdrawn. Nutrition was thought, in many cases, to be markedly improved, as when blood was carefully withdrawn the appetite improved as did also digestion and assimilation; small and frequent bleedings served to calm the circulation and this condition favored the deposition of fat; absorption from cavities and the interstices of the body was increased, hence the relief of dropsies and inflammatory exudates; the brain was thought to have its sensibilities to all kinds of impressions increased, while the power to act with effect and continuously was diminished, the mental powers were not thought to be impaired. It was considered "highly necessary to attend to the state of the mind and feelings of the patient" as "in persons of a timid disposition, the bare proposal of the operation of bleeding or even expectation of it, will sometimes occasion such general disorder of the system and in the pulse more especially, as may lead us to form an erroneous opinion as to the existing malady and its treatment." [11]

Blood-letting was used for a threefold purpose, as a curative, as a palliative and as a preventive. "In regard to its curative powers, blood-letting is capable of removing, with more or less facility, though never perhaps with absolute certainty, a great number of diseases, which but for its aid, would endanger or destroy life, and which cannot be effectually combated by other

[9] Magendie, F.: The Blood, p. 96.

[10] Idem: p. 97.

[11] H. Clutterbuck: Lectures on Blood-letting, p. 25.

means. Considered in the light of a palliative merely, it is still of no small value . . . . there are scarcely any that do not admit of more or less palliation; and blood-letting is often the best means we have of effecting this purpose. An instance of this is afforded in the case of phthisis pulmonalis, where the acute pain that occasionally arises in the chest, even in an advanced stage of the disease, and when the case is altogether hopeless, seldom fails to be relieved by a small bleeding; and (provided this be done under proper limitation) without any increase of weakness, or other inconvenience. On the contrary, not only is the pain relieved, but the hectic and night sweats also; while the appetite is usually improved by it, and sleep rendered more refreshing. The same remedy is also, on many occasions, preventive in its effects; by lessening if not destroying the tendency to certain diseases, of which apoplexy, hemorrhage and inflammation may be cited as examples sufficiently well known."[12] It was believed to be capable at times of controlling spasm, to act as an anodyne in the relief of pain and as a narcotic inducing tranquil sleep. It was used to influence disease in one or more of the following ways: by merely reducing the mass of blood, by a general weakening of the system and as a sedative by diminishing vascular activity and excitement. The first was used to overcome that factor which was thought to hold such a very important position in the cause of disease, regardless of its nature, namely *plethora;* the second to overcome what was known as the *sthenic* condition, which was thought to call for a weakening of the system, and in cases of fever and vascular excitement blood was drawn for its sedative effect.

Blood was obtained in one of four ways and much discussion was indulged in in regard to their relative values; phlebotomy or the opening of a vein, arteriotomy or the opening of an artery, scarification, either with or without cupping, and by the use of leeches. Phlebotomy and arteriotomy constituted what was known as general, and scarification and leeches what was known as local or topical bleeding; the former was supposed to produce its remedial effect "either by sympathy or through the medium of the general system" and in the latter "the blood is taken, or presumed to be taken, immediately from the vessels of the diseased part or those in its immediate vicinity." Two conditions were chiefly relied upon in determining how and in what quantity blood should be taken, the strength or weakness of the patient and the condition of the pulse. Dr. Clutterbuck concludes a very interesting discussion of the pulse as a determining factor in blood-letting as follows: "There is, nevertheless, a state of pulse that is always extremely unfavorable to blood-letting, if not altogether prohibitory of it: I mean, where it is at once small, soft and compressible by the slightest force. But this is sure to be accompanied by other unequivocal signs of extreme weakness that cannot well be mistaken.

"Upon the whole, I may observe, that there is hardly any condition of pulse, either in regard to strength or weakness, fullness or smallness, hardness or softness, frequency or slowness, regularity or irregularity, which taken singly and in all cases, either absolutely calls for, or prohibits, blood-letting. Much attention, doubtless, is due to all of them. Each may serve as a guide, in regard to the quantity of blood to be drawn, the repetition of the operation and the like; while, taken in conjunction with other circumstances, it may serve to determine the propriety of the evacuation altogether."

The questions to be answered in each case, after a bleeding was decided upon, was how much and in what manner the blood should be taken. Much discussion took place as to whether there should be one large bleeding or several small ones, and the celebrities of that day were frequently called in consultation to determine the point.

In adults of good general health, from 8 to 12 ounces was considered a moderate and 16 to 20 ounces a large bleeding. The large bleedings were, as a rule, resorted to in the acute and violent types of disease and the smaller in those types of a more chronic character.

Dr. Rush, of Philadelphia, says that 90 ounces were taken at one time from his friend, Dr. Dewees, and with advantage. The latter physician, Dr. Dewees, himself states that he took 80 ounces of blood within a few hours from a young and delicate woman, who had been seized with convulsions towards the end of pregnancy; and from another similarly affected, at the commencement of labor, he drew 120 ounces within five or six hours, and 20 more the following day. The patient, notwithstanding, he says, recovered rapidly, but became blind and continued so for a fortnight and did not perfectly recover her sight for six months"[13] "Dr. Barlow . . . . mentions the case of a feeble and emaciated boy, who was laboring under diabetes, and from whom 209 ounces (13 pounds) were taken at 12 successive bleedings, in the space of 51 days, which is at the rate of 19 ounces each bleeding; he was bled twice a week on the average. The effect, Dr. B. says, was striking; from a state of feebleness, hardly admitting of an erect posture, the lad acquired a degree of vigor which enabled him to hold the plough for several hours a day."[14]

Blood-letting, above all, was used in that strange series of phenomena which grouped together were called inflammation. Dr. Clutterbuck says, p. 60: "Among the diseases to which blood-letting is particularly adapted inflammation undoubtedly claims the first place, for it is here that the power of the remedy is most strikingly displayed, and its employment the most frequently called for." Again, p. 65, he says: "Different circumstances appear to influence the result, in the application of blood-letting as a remedy for inflammation, and which, therefore, require to be considered. The following are the chief:

"1. The degree of the disease.

"2. The stage of it.

"3. The part in which it is seated.

"4. The nature of the inflammation itself."

Hemorrhages of the so-called active type were treated to a very large extent by blood-letting, as were also dropsies. Many

[12] Idem: p. 27.

[13] Idem: p. 51.

[14] Idem: p. 52.

forms of cerebral disease were thought to be very favorably influenced by the drawing of blood, notably apoplexy.

This imperfect sketch may be fittingly concluded by a quotation from Dr. Clutterbuck; he says, p. 36: "There is no one function, either mental or bodily, that is not more or less under the immediate influence of this agent, according to the manner in which it is applied, and the extent to which it is carried. It quickly and powerfully disturbs the heart and whole vascular system; as is evident not only from the changes induced on the pulse but from the capillaries, in extreme cases, suddenly ceasing to contract, so as to allow their contents to escape in the form of cold sweats; respiration is disordered by it—the alimentary canal and urinary organs often discharge their contents involuntarily—and lastly, the cerebral functions of sensation, voluntary motion and thought, are impaired, disordered or even wholly suspended, by a sudden and copious abstraction of blood. Nor are morbid actions by any means exempt from this influence (for disease is only a modification of healthy action, and is more or less under the influence of the same agents). In short, blood-letting, in checking or suppressing violent diseases of any kind, appears to act upon a principle very analogous, if not identical with, what is called counter-irritation, but which in this case is, perhaps, better termed counter-impression."

THE IMPORTANCE OF A THOROUGH TEACHING OF INFECTIOUS DISEASES OF CHILDHOOD IN THE MEDICAL CURRICULUM.

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The average student leaves our medical schools without having seen many of the infectious diseases of childhood. When entering on his practice, his ignorance contrasts sadly with the knowledge of mothers and grandmothers gained by experience.

Several reasons may be assigned for this apparent neglect of a thorough instruction of our medical students in these diseases. A large number of medical schools have no hospitals of their own in which the teaching could be carried on in a way satisfactory to the faculty. Those medical schools which are more intimately connected with well equipped hospitals labor under the disadvantage that these hospitals do not admit cases of infectious diseases. One of the most prominent reasons for such a policy is the expense, which is necessarily caused by the proper care of these cases. The most important consideration which confronts those in charge of the hospitals is, not to expose the other patients to the danger of infection. This can only be accomplished by having a number of rooms at disposal where suspicious cases can be watched, and special wards where positive cases can be kept without danger to other patients. The proper construction of such wards insuring the necessary isolation of the patients with the increased demands for cleaning and disinfecting, exceeds the means of most of our institutions. Aside from the separate construction, the service is necessarily connected with great expense. It requires a special set of nurses, and the staff of nurses must be kept up even with a relatively small number of patients. Not only the patients suffering with various infectious diseases must be kept apart, but the nurses of the different wards cannot be interchanged. For instance, a ward where scarlet fever patients are kept may be filled, and this necessitates an addition to the staff of nurses, while in the ward for diphtheria there may be only one or two patients, but the nurses assigned to the diphtheria ward cannot be called to service in the scarlet fever ward.

For these reasons mainly, the medical schools lack the necessary material, under their own control, for teaching. This lack could be supplied in certain communities by utilizing the special hospitals for infectious diseases, which are usually city institutions. Sometimes the rivalry between the medical schools in a given community prevents the proper utilization of these opportunities; sometimes these hospitals are rather far distant from the centers of medical learning and this creates new difficulties.

Many communities insist that a hospital for infectious diseases ought to be removed beyond the boundary line of the city. This is certainly just for those infectious diseases which do not occur regularly in the community, for instance sporadic cases of certain infectious diseases introduced from outside. This requirement is absolutely justified in cases of plague, cholera, small-pox, etc., but there is absolutely no necessity, and we may perhaps say that it is not reasonable to adopt blindly such strict rules for infectious diseases which occur constantly in our own midst, where in the majority of cases many foci of infection still remain within the city limits, for a certain number of cases are taken care of at home, light cases are frequently not recognized, and in many instances the infection is spread far and wide before the label is put on the door.

In fact, we have to distinguish accurately these two kinds of infectious diseases: sporadic infections from outside which can be kept from the community by a rigid legislation, and endemic diseases in which the scope of the legislation is only to take care of the individuals, and to avoid further infections as much as possible under given conditions. For the first kind of diseases the utmost strictness should be applied. For instance when a case of plague is reported, not only the patient himself must be taken to an absolutely isolated hospital, but also all persons who are likely to have become infected by him should be kept under observation for a certain time. On the other hand, chicken-pox, for instance, is such a generally spread and at the same time mild infection, that it is a waste

of money to apply any elaborate hygienic measures to treat the comparatively few cases which are brought to the notice of the health authorities. Now between these two extremes, every other infectious disease must be considered individually, depending on its gravity, its infectivity, and the fact whether at the place in question it is endemic or sporadic. Let us suppose, for instance, an island to which measles is brought only every twenty or thirty years. Here a case of measles should be treated under the strict rules given for an outside infection which can be controlled. On the American and European continent, however, any attempt to really control measles is a futile one, since thousands of foci always exist.

It is very interesting, nevertheless, to think that just in measles it would be possible to get rid of the disease entirely within three weeks if at some time the whole earth should be under exact hygienic regulations. Suppose in all countries such hygienic measures would be possible as is the case in the most civilized ones, and for only three weeks every patient with measles could be kept apart from those persons who did not yet have the disease, we would get rid of it with one stroke, as there is no probability that germs of measles can be transmitted to animals, and as they do not stand drying. Every infection is given from man to man, and the infectivity of the cases lasts a very short time, probably only about a week after the outbreak of the rash. So, if for three weeks no new medium was offered to the germs, they would necessarily die out. But this is a dream of the future.

I started to say that the same hygienic rules are not to be applied in all infectious diseases, and that it is not objectionable at all to have wards for the common endemic diseases within city limits, for the purpose of teaching and also for the reason that parents are nearer to their children. The necessary consequence of an infectious hospital outside of city limits is that parents do not like to give up their children, and therefore conceal an infection as long as possible. In mild cases this can easily be done by not calling a doctor, and then just the opposite of the hygienic measure intended is a practical result of it, *i. e.*, that no attention whatever is given to the spreading of the disease. This idea of not allowing any infection within city limits reminds me of a city in Russia, where the council wished to build a sewerage system. All the proprietors of the houses where the canal was to be built objected to being in the immediate neighborhood of the system on account of the bad odor, which they supposed would be a necessary consequence. But the material is in town, and how can it be carried out without a canal? That is not our affair they answered, the only thing we say is that we will not allow anything called a canal to pass our houses.

That is not so different from our subject as it seems at first sight. The infectious diseases are endemic in town, we cannot deny that; every street contains foci, and if we include tuberculosis among the infectious diseases, we may say that every house contains infectious agents. The sewerage of infections of that kind must be made so easy, that people in their own interest shall prefer to use it. If we force every infection, which is declared to be one, far out of town, if we do not allow the parents to visit their children there, the natural consequence is that the parents will use that hospital as little as possible, and that, if they know that a doctor applies all hygienic measures, they will simply not call the doctor, but help themselves in another way, dangerous not only for the patient but for the neighborhood. I can give you examples from Vienna, where infectious wards are connected with each of the children's hospitals, and there are in addition, two large hospitals for contagious diseases outside the limits of the city. The parents come very often to ask whether there is a place in one of the town hospitals; if there is not, they object to having their children taken to the out-of-town hospitals, as they are so far away that a visit there is difficult and furthermore costs the parents a half-day's salary. There is besides another disadvantage in cases of diphtheritic croup. Every year cases of death from suffocation occur, caused by the delay in carrying the children from their homes or from the out-patient department of another hospital to the very remote infectious hospitals.

As to the danger of a hospital for these common infections being within the city limits, there is none at all for the neighbors, if care is taken, and I do not remember any case of infection of a child due simply to the neighborhood of these wards. Every out-patient department is far more dangerous, where children wait together before they are classified, and in every car where children ride together to a hospital, there is more likelihood of an infection, than in the surroundings of a closed building containing carefully watched cases of infectious diseases.

In those cities where infectious hospitals have been established lately within city limits, the effect on the number of infections and on their gravity has made itself felt strikingly by the diminution of these diseases. I have been told of Boston that the health authorities there are extremely satisfied with the results of that system.

In New York also the system of in-town infectious hospitals works very well; and Dr. Biggs told me lately, that they have even allowed the parents to go in the wards to visit their children under certain hygienic precautions. This is also done with the idea of making it as easy as possible for the public to use the infectious hospitals. The result is that an ever increasing percentage of cases are sent there, that they are treated better, and moreover that they do not infect others.

The ideal condition would be to have all of the cases of certain infections treated in hospitals, namely, scarlet fever, diphtheria and whooping cough. The reason for scarlet fever is that the germs are extremely stable, and that in an ordinary room of a private house where a scarlet fever patient has scaled for several weeks, one can hardly make a perfect disinfection. There are cases reported of children who apparently got scarlet fever in a certain room of a house at intervals of many months.

The contamination may be on other objects which at home are not always really disinfected. I saw the following instance: a girl of four years died of scarlet fever; the clothes were disinfected, with the exception of a little fur coat and

fur cap which were not delivered to the disinfector by the mother, as she feared that they would be damaged. She kept them in a box in the house, and took them out only after two years when the next girl was old enough to wear them. Four days afterward the girl became ill with scarlet fever. Therefore, we should send scarlet fever patients to hospitals to prevent the infection of rooms and objects.

In diphtheria it should be done as there is always a possibility that laryngeal symptoms may develop. Every case which does not come very early under the doctor's care and where no anti-toxin injection has been made at once is better off in a hospital under constant observation.

As to whooping cough, only extensive hospital accommodation will allow us to master this dreadful enemy of childhood. At home we cannot keep the children in the room for such a long time: they go out on the street, to the parks, and always infect others. Large wards should be constructed for these children, it would be well to send the convalescents to a farm.

So, hospital treatment is wanted for the sake of the public in scarlet fever and whooping cough on account of their infectiousness; in diphtheria on account of its immediate danger and sequelæ for the child.

We must look in quite another way at measles, German measles and chicken-pox. Chicken-pox is a milder infection than an ordinary coryza, and it is practically not worth while to adopt any isolation measures; the same is true for German measles. In measles hospital treatment gives, on the whole, worse results than treatment at home, due to the secondary infections which are apt to follow. If in a hospital the accommodations are not very extensive, the children with measles easily get secondary broncho-pneumonia and other infections in the ward, especially influenza or diphtheria, if one of the other children in the ward happens to have it. The statistics show better results in the cases treated at home.

Here two reasons may be given for hospital treatment of these diseases; first, the necessity of caring for those cases which cannot have the proper treatment at home; and, second, the necessity of studying those diseases and of instructing students in them. For these purposes cases of stomatitis, aphthæ, Vincent's angina, etc. would also be accepted. These diseases do not require an entire ward to themselves, but merely cubicles separated by glass partitions according to the French system, with of course a careful, separate service sufficient to avoid spreading of the infection.

The infectious disease of childhood which has the most severe consequences for a lifetime is certainly tuberculosis. We know that most of us are infected during childhood, and probably the pulmonary tuberculosis of adults is only a recrudescence of the early process, comparable to the third state of syphilis. Only about seven per cent of the tubercular infections are fatal. It is quite wrong to close our eyes to the truth, as for instance with the sewerage example, and to declare only those people tuberculous who after some examination are so labelled. It is of the utmost importance to make it as easy as possible for the carrier of lung foci, who spits and coughs tubercle bacilli, to be received in wards within the city limits, but under hygienic conditions, and thus prevent their spreading the disease by reckless spitting. This question has been referred to lately so many times that I will not delay over it, but only say that it is extremely necessary that special wards for tuberculosis should be attached to teaching hospitals, and that every means should be taken to exterminate the disease wherever it is found.

But now some one will say is it at all worth while to fight the common infectious diseases? Isn't it simply a matter of chance whether a child will get it or not, and isn't it even better for the child to have it early? Many people have an idea with regard to infections somewhat related to the theories of the old Indian brahmins on small-pox. These old colleagues thought that every man had in himself small-pox stuff, and that the infection consisted only in the act of setting that stuff on fire. It was best for the stuff to be lighted at a given age and under good hygienic conditions, so that the necessary blaze should not create too much trouble in the organism. This was the idea which led to small-pox inoculation, the method of which is preserved in our vaccination. With vaccination we let every individual pass through a mild form of the disease. Is this not ideal for all the infections? No, as on one hand we are not yet far enough advanced to vaccinate against every infection, and on the other hand it would not even be practical for all of them. In this respect also we must individualize entirely according to the diseases. There are only a few maladies which are so infectious for all ages that the probability of becoming infected sooner or later reaches about 90 per cent. This was the case with small-pox in former centuries and is nowadays the case with measles. These are diseases for which the disposition does not change during life. In the Fiji Islands, for instance, where a measles infection entered in 1875, after the last epidemic had occurred in 1846, practically every person became infected, the old people excepted who were immune from the first epidemic thirty-nine years earlier. In America and Europe the possibility of becoming infected is such that we cannot protect children absolutely from measles, for they will become infected sooner or later, and all we can hope for is that the whole family may chance to get it at one time when the hygienic conditions are favorable.

But quite different are the conditions in scarlet fever and whooping cough. Here the disposition diminishes in later years of childhood. Scarlet fever does not attack a great percentage of people, and the immunity of later life consists not only in a personally acquired one, as is the case in measles, but the disposition decreases with age. Here we should make every effort to avoid infection, for as the child grows older, the probability of its getting the disease becomes less. The conditions in whooping cough are similar, and especially chicken-pox, which is hardly infectious for adults.

A third group of infectious diseases leaves no immunity, and, therefore, an infection in childhood does not eliminate the chance of a later attack. This is the case in erysipelas and in diphtheria. But in diphtheria the general disposition diminishes as one grows older, and especially the disposition

for the laryngeal form. So, if possible, it is wise to avoid exposing children to this disease.

The hygienic measures which the Board of Health enforces on the family of the patient should be varied in accordance with the different diseases; for instance it is not justifiable to restrict the movements of the inmates of a house harboring a case of measles, and the necessity of disinfecting the rooms where such a patient has been kept is much less important than the disinfection of a room of a scarlet fever patient.

As to the *teaching of infectious diseases,* we must again make the separation of the two main groups. To the one belongs the sporadic infections not endemic in a community; to the other, the common infectious diseases. With regard to the first group a thorough knowledge of the diseases no doubt is desirable but practically impossible, as the student never will see many, if any, cases of these rarer infections. The student must be taught the principal features of such diseases, and he must be impressed with the fact that his knowledge of these diseases is by necessity deficient.

But what we must demand from the practitioner is that he be well enough acquainted with the usual infectious diseases, so that if he sees a case of one of the rarer infectious diseases, if he happens to meet it in his practice, he may recognize that it shows some features which do not belong to the common infectious diseases and know that the patient should be at once isolated; for instance it cannot be expected that the average practitioner should recognize immediately a case of small-pox at its onset, but it should not happen—as has occurred lately—that a case of small-pox is mistaken first for a case of measles, then after the lapse of a few days for one of chicken-pox. It the practitioner is confronted with an unfamiliar exanthematous disease, he should know enough not to be ashamed of his limits of knowledge, and call to his aid the proper health officer, of whom we presuppose a thorough training in all infectious diseases. If the training of the practitioner has been proper, he will not hesitate to avail himself of such an opportunity.

With regard to the teaching of the common infectious diseases, it is not sufficient to have read the text-books or to have seen as many cases as even a man with a large practice may see. The infinite variety of the manifestations practically precludes the possibility of seeing enough of these cases in a practice ever so large. If we expect a thorough training of our students within a relatively short time, we must demand from the teachers of this subject a further knowledge than text-book and private practice can supply. Only a special training in infectious hospitals can give the teacher sufficient experience to instruct the student properly.

Naturally with the time allotted for the study of our subject, it will never be possible to show the student all the varieties of the different diseases, but having had a proper training himself, the teacher will be capable of insisting on the most essential features and the occurrence of certain so-called abnormalities in the course of the disease, and of calling attention to others which may occur. We need not dilate on the fact that the course of the infectious diseases is just as frequently atypical as typical. It is of great importance that the student should follow the cases from beginning to end, so that he may learn to distinguish rapidly the different phases in which a case may be presented to him. At the same time it is only in this way that it is possible for him to study the effect of therapeutic measures, and the results which he may expect from them.

One of the most frequent questions which will be asked in medical practice is, how long will the disease last, and what will be the probable outcome? It is impossible to gain enough information about the different phases and possibilities of the diseases by the uncertain observations in a dispensary, and while we all know that the practice must fill out many a gap in our medical school education, it would be very desirable not to leave too big a gap in a field of such importance. Whereas therapy can be learned more or less from books, the decision whether a case is dangerous or not rests upon personal experience.

The *teaching of diphtheria* will have to do first with a quick and sure diagnosis. The first symptoms here often arise so slowly and with only general indisposition, that a doctor who is not accumtomed, on principle, always to look in the throat of the child, easily overlooks the first stages. The student must be taught to look in the throat of the child, because this is not so easy a matter, especially in private practice, and sometimes one is compelled to use various tricks. Then it requires a certain experience to see at a glance the slight gray spots on the back wall of the throat for example, which are so characteristic of diphtheria; one must become accustomed to the importance and nearly decisive meaning of a simultaneous hoarseness and angina, and of a discharge from the nose due to diphtheritic infection.

Besides the diagnosis by sight, the student must become familiar with the aid the laboratory lends to the diagnosis. If a case shows a gray membrane, or a combination of angina with hoarseness, or one has some other reason for making a clinical diagnosis of diphtheria, one should never wait for the result of a bacteriological examination, but inject the serum; only in slight and doubtful cases one may wait with the treatment. Before reporting a case as one of diphtheria we may wait until the diagnosis is more firmly established in order not to cause trouble when one is not absolutely sure that the case is really one of diphtheria. The technique of serum injections must be taught furthermore, and the rashes due to horse serum, so that they may not be mistaken for scarlet fever or some other complication. The immediate anaphylactic phenomema which may occur if a patient is injected a second time with horse serum must be also familiar to the student.

Very important is the treatment of croup. We first use in every case the ingenious discovery of O'Dwyer, the intubation; only if that fails, because the membranes extend down too far, do we try a tracheotomy. Intubation should be taught to every student, either by means of the cadaver or of models. It is an easy and quick operation for the man who has learned

it, but it is difficult to perform for the first time in an urgent case in the moment of suffocation.

The sequelæ in diphtheria must be known: the danger of heart weakness, the symptoms of it, the comparatively unimportant albuminuria, and the many kinds of nervous and muscular troubles during convalescence.

In *scarlet fever* the diagnosis of the exanthem is a thing which we never can learn absolutely. Typical cases are easily recognized, but there are so many forms that only a good experience gives some degree of certainty. How many cases of mild rashes are considered as exanthemata due to heat and neglected, and three weeks later the kidney trouble sets in! And how much harm is done if only the throat is inspected and not the body! As to the prognosis, we shall have to tell the student that every mental trouble or delirium, for instance, bodes ill in scarlet fever, and that the temperature is intimately connected with the intensity of the case; whereas in diphtheria the height of the temperature means nothing, as the worst cases may show a subnormal temperature.

In *measles*, again, the temperature is always a very high one; it means nothing as long as it precedes the outbreak; if it does not disappear, however, three days after the beginning of the rash, we know that some secondary infection has occurred, and we should make a very careful examination of chest, throat, nose and ears. Here the students need not only be taught the exanthem in its various forms, but especially the very characteristic symptom of the mucous membrane of the mouth which we owe to Koplik, enabling us to form an absolutely certain diagnosis generally two days before the exanthem—two days before the mother and grandmother make their diagnosis. The connection of measles with tuberculosis is of great interest.

In *chicken-pox* we must make the differential diagnosis from impetigo on one hand and from small-pox on the other.

In *tuberculosis of childhood*, all the various and numerous forms must be watched and the modern methods of diagnosis be taught. Then only do we see what an enormous part this disease plays among the anemias, skin diseases, and eye diseases of childhood. The first signs of a miliary tuberculosis especially should be noticed, and the picture of a beginning meningitis impressed on the student; for this is a disease where a wrong diagnosis is often held as a long lasting reproach against the doctor by the parents. The practice of lumbar puncture is necessary both for tubercular and *epidemic meningitis*; and here we should also teach the intraspinal injection of Flexner's serum. An exact differential diagnosis between the main kinds of meningitis is extremely necessary for the prognosis and for the therapy.

Finally, very easily taught and extremely important for the conception and clinical understanding of infectious diseases, is the *cowpox vaccination*. Here we produce a real infection on the skin and see its whole development, see the influence on the general system, and can study the effects of immunity in watching carefully the results of a second vaccination. This simple operation should not only be taught as a matter of routine, but as a deep and interesting experimental study of the forces of the organism against the microbe.

To sum up, we reach the conclusion that the medical student should get a good training in the ordinary infectious diseases of childhood, in order to make the diagnosis with certainty, even in somewhat atypical cases, in order to apply the right therapy, to be able to make a prognosis, and in order to take prophylactic measures necessary in the case of special disease; finally, in order to recognize a case of an unusual infection which may mean a real danger for the community.

For this purpose it is not sufficient for the student to get a theoretical course or to see a case in a dispensary now and then, but the student should be taught by the bedside and by a teacher who has himself a thorough training in infectious diseases. To this effect, wards for the common endemic infections should be attached to the hospitals of the medical schools. This is not only not objectionable from the hygienic point of view, but has many advantages. A certain number of hours of bedside instruction in infectious diseases should be inserted as a necessary course in the medical curriculum in the third or fourth year.

I hope that the audience will endorse the importance of these demands, and that the American Medical Association will take up the matter and bring it to the general consideration of the profession.

NOTES ON NEW BOOKS.

St. Louis. Its History and Ideals. Prepared for the Sixty-first Annual Session of the American Medical Association by PHILIP SHRAINKA, M. D. (*St. Louis, 1910.*)

An excellent guide to the city, well illustrated, and serviceable for all visitors.

La tension artérielle en clinique, sa valeur séméiologique. By DR. LOUIS GALLAVERDIN, Medecin des hôpitaux de Lyon. (*Paris: G. Steinheil, 1910.*) 206 pp. 69 figures.

This little book deals only with clinical hydrodynamics, the technique of the various clinical methods of sphygmomanometry and the principles on which their use is based. In this respect, in text, figures and bibliography it carries out very well the intentions of the author and furnishes interesting and profitable reading to any one who desires to become thoroughly acquainted with clinical hæmodynamics. Unlike many books written upon the continent, the English and American literatures are discussed along with the French, German and Italian. The conditions in which disturbances in arterial blood pressure occur and the discussion of venous pressure do not fall within the scope of the book.

American Practice of Surgery. Editors: JOSEPH D. BRYANT, M. D., LL. D., ALBERT H. BUCK, M. D., of New York City. Complete in eight volumes. Profusely illustrated. Volume seven. (*New York: William Wood and Company, 1910.*)

With the exception of one chapter on the Surgery of the Pericardium, Heart, and Blood-Vessels and one on Surgical Diseases of the Extremities, this volume of over 950 pages is devoted to the

affections of the abdomen and pelvis. The surgical diseases and wounds of the œsophagus are treated with those of the stomach. The sixteen chapters have been written by sixteen authors—surgeons widely scattered through the United States, so that the work is really representative of "American Practice." A general country surgeon must necessarily have some such work on his book shelves, and whether he buys this system or the one lately edited by Keen will depend almost entirely on his personal preference and opportunity to compare the two. Both will prove of service to him, and with either he should be well contented. They, neither of them, can replace well-written monographs, or volumes devoted to special regional surgery, but for those he will probably have less call than for the larger systems, burdensome as they are, by their size. With this "Practice" at hand a surgeon should seldom be in doubt as to a safe method to pursue in a given case, but no book will serve him in every instance, and he must be ready to use his common sense in emergencies, which after all is his most serviceable tool, when he is once grounded in the principles of surgery.

Diseases of the Stomach and Intestines. By Robert Coleman Kemp, M. D., Professor of Gastro-intestinal Diseases, New York School of Clinical Medicine. Octavo. Illustrated. Cloth, $6.00. (*Philadelphia and London: W. B. Saunders Company, 1910.*)

This book as the author states in his preface is designed to present simple and practical methods to the general practitioners and this it does very well.

The anatomy and physiology of the stomach and intestines are first considered and the general methods of physical examination detailed with chapters on the X-ray and transillumination of the stomach, the use of various test meals, etc. Diet and therapy, with the use of electricity massage and hydrotherapy are fully dealt with.

The various diseases of the stomach are next taken up in detail and the functions of the stomach in diseases of the organs dealt upon.

Diseases of the intestines follow in the last half of the book and methods of examination detailed; among the diseases considered, there are special chapters on dysentery, typhoid fever, appendicitis, diverticulitis and intestinal parasites.

The book as a whole seems to accomplish very well certain of the author's ideas expressed in the preface, but at times strives to accomplish too much in a small space. The practical side of the subject is, however, well borne in mind throughout and the illustrations quite good (except for the tendency so prevalent at present of using *female models* to illustrate either unimportant points, or points that at least could be much more clearly and accurately shown on a diagrammatic figure).

Urgent Surgery. By Felix Lejars, Professor Agrégé à la Faculté de Médecine de Paris, Chirurgien de l'Hôpital Saint-Antoine, Membre de la Société de Chirurgie. Translated from the sixth edition by William S. Dickie, F. R. C. S., etc. With 20 full-page plates and 994 illustrations, of which 602 are drawn by Dr. Daloine and A. Leuba, and 217 are from original photographs. Vol. 1. (*New York: William Wood and Company, 1910.*)

The author says Urgent Surgery does not mean merely the surgery of injuries, but also includes the numerous clinical conditions which demand immediate surgical action.

He thinks that those who are not operators themselves should at least know something of the details of the operation. Also that there are certain things which every practitioner should be able to do, and which he cannot avoid without dereliction of duty.

He says that in this book there are no theoretical discussions or descriptions of untried methods.

Urgent operations and procedures are taken up and are described as the author has found it most expedient in his experience.

There have been 6 French editions in ten years and the work has been translated into German, Spanish, Italian, Hungarian, Russian and Japanese, which shows its popularity.

This volume is divided into six sections, as follows: I. Introductory; II. The Head; III. The Neck; IV. The Thorax; V. The Spine; VI. The Abdomen. The book shows the operative methods of a French surgeon in treating lesions which are of the greatest interest to every general surgeon.

The translation has been especially well done, and the volume has lost nothing of its effectiveness in the hands of the translator. The book is well gotten up, the illustrations are good.

While it is doubtful whether the general practitioner should ever operate for most of the conditions described, nevertheless a careful study of this work will be of great advantage to the practitioner, but more especially to the practical operating surgeon.

J. S. D.

Bulletin of the Warren Anatomical Museum. Harvard Medical School. No. 1, Pathological Anatomy—Bones, Joints, Synovial Membranes, Tendons. (*Boston, Mass., 1910.*)

Dr. William F. Whitney, the curator of the museum, has prepared admirably this first Bulletin to be followed by others, and which will perfect little by little the original catalogue first published many years ago. There can be no doubt that if these Bulletins can be freely illustrated they will prove serviceable to many men and in many ways. This number contains some excellent reproductions, and is of special interest to the orthopedic surgeon. It is not intended to catalogue every specimen but to issue Bulletins of different parts of the collection. The contents of No. 1 include under the heading of bones, specimens of osteomyelitis, tuberculosis, scoliosis, club-foot, etc.; and under joints, specimens of spondylitis, and arthritis deformans, and gout; under synovial membranes, simply joints and bursæ are mentioned.

Department of Commerce and Labor. Bureau of the Census. C. Dana Durand, Director. Mortality Statistics, 1908. Ninth Annual Report. (*Washington: Government Printing Office, 1910.*)

The value of these reports increases annually from the larger figures which are dealt with and the greater elaboration in the preparation of the tables. Since the last report two new states are now included among the registration states so that just over one-half the total estimated population is now represented, and when the next report is issued a still larger proportion of the population will be represented. The "Introduction" by the Director is full of interest to all those working for the national welfare. Not only statisticians but doctors should read it carefully, and to all Boards of Health the statistics are of the utmost importance. The Director has carefully analyzed the mortality figures from the leading causes of death, and his "Introduction" is not "dry," even though dealing largely in numbers, but on the contrary is so full of thought and information, that its careful study is repaying.

Medical Electricity and Roentgen Rays with Chapters on Phototherapy and Radium. By Sinclair Tousey, A. M., M. D. (*Philadelphia: W. B. Saunders & Co., 1910.*)

In a new branch of medicine and one which is developing so rapidly and along so many lines it is a difficult proposition to present the subject in a systematic way. The author, however, has succeeded remarkably well in giving us a clear and concise presentation of the subject. The book is divided into three sections, namely Medical Electricity, Radiography and Radiotherapy, and Radium.

Two-thirds of the book is given over to Medical Electricity. It gives the elementary principles, the mechanism and the methods to obtain the best results. Possibly the author may be somewhat

over-enthusiastic in his claims for the therapeutic effects of electricity in certain diseases, yet as a whole he has been quite conservative.

The section on Radiography and Radiotherapy is excellent. The author is especially to be commended for his advocacy of the fluoroscope. Fluoroscopy, especially in this country, has been much neglected in recent years on account of the fear of dermatitis to the operator. With proper care this can be avoided. A thorough examination of the chest is incomplete unless fluoroscopy is employed. It is the only means whereby we can see the viscera in motion. To see the definite limitation of motion of the diaphragm or the clavicles in pulmonary tuberculosis, when the lower or upper lobes are involved, will convince one immediately of the value of this method. The author has emphasized this point.

In the section on Radium the chemical and physiological effects are given and theory of radioactivity. Then we have a short account of the pathological and the therapeutic uses. This section is naturally brief as the high cost and scarcity of radium has limited its use to but a few experimentors and consequently the data is necessarily small.

Preparatory and After Treatment in Operative Cases. By Herman A. Haubold, M. D. With 429 illustrations. (*New York and London: D. Appleton and Company, 1910.*)

The book is divided into 34 chapters, the first 15 of which consider sterilization, materials, etc., and the general subject of preparatory and after treatment. In the remaining chapters the preparatory and after treatment of operations on the different regions of the body are taken up.

The book is clearly written and is well gotten up. A number of authors are mentioned and quotations from their papers are used, but very few of the original references are given. The illustrations are good but considerably more than half of them are taken from other articles or from instrument catalogues.

It is the desire of the author to furnish "a work from which the practitioner can draw information with regard to the handling of a case to be operated upon from the time the decision to operate is reached up to the making of the incision, and then take up the case again from the time the operative technic is ended until recovery is complete."

The volume accomplishes this object, and will be of more use to the practitioner than to the surgeon. J. S. D.

Myomata of the Uterus. By Howard A. Kelly and Thomas S. Cullen. Illustrated by August Horn and Hermann Becker. Price, $7.50. (*Philadelphia: W. B. Saunders Company, 1909.*)

The authors present in attractive form an exhaustive clinical and pathological study of 1674 personal cases of uterine myomata, observed, studied and treated in the Gynecological Clinic of the Johns Hopkins Hospital and in their private practices. The autopsy material at the Johns Hopkins Hospital has been utilized in the chapters on the frequency of myomata and on their association with pathological conditions in other organs. Including its index the volume contains 723 pages. There are 388 illustrations.

The highest praise should be accorded the publishers for the way they have printed the text and reproduced the superb drawings of Messrs. Horn and Becker. The paper is thick, the print large and clear and the illustrations unusually plastic, an affect attained by a brown ink which, so far as is known to the reviewer, has never before been employed for the illustrations of a medical work.

The book is divided into 35 chapters, the titles of which afford an insight into both the matter treated and the method of treatment. In Chapter I, "Uterine Myomata," their site, number, size, shape, blood supply, histogenesis, relation to the body of the uterus and condition of the myometrium are considered. To Chapter II, "Parasitic Uterine Myomata," nearly forty pages is devoted. It is clear, complete, new and beautifully illustrated. Chapter III fully deals with "Cervical Myomata" and the illustrations are fine. Chapter IV discusses "Submucous Myomata" and especially those undergoing necrotic change and sloughing. Chapter V, "Dilatation of the Uterine Lymphatics Associated with Myomata," brings to the reader's attention in clear and graphic form a condition not generally appreciated. Chapter VI, "Torsion of the Uterus." Chapter VII, "Hyaline and Cystic Degeneration." Chapter VIII, "Calcification of Uterine Myomata." Chapter IX, "Suppurating Uterine Myomata." Chapter X, "Myomata Associated with Malformations of the Uterus" affords some interesting examples of this unusual association. We would suggest that this chapter would have been placed better as Chapter XIV. Chapter XI, "Angiomyoma." Chapter XII, "Lipomyoma of the Uterus." Chapter XIII, "Adenomyoma of the Uterus." Chapter XIV, "Myosarcoma of the Uterus." Ninety-three pages are given to this important subject, which is treated lucidly. Chapter XV, "Carcinoma of the Cervix Associated with Uterine Myomata." Chapter XVI, "Adenocarcinoma of the Body of the Uterus Associated with Uterine Myomata." Chapter XVII, "The Condition of the Uterine Mucosa in Cases of Myoma." Chapter XVIII, "Conditions of the Tubes and Ovaries when Uterine Myomata are Present." Chapter XIX, "Conditions Found in the Ligaments Passing to and from the Uterus in Cases of Uterine Myomata." Chapter XX, "The Bladder in Cases of Uterine Myomata." Chapter XXI, "The Ureters in Cases of Uterine Myomata." Chapter XXII, "The Rectal Findings in Cases of Uterine Myomata." Chapter XXIII, "Analysis of the Causes of Uterine Myomata Found at Autopsy in the Pathological Laboratory of the Johns Hopkins Hospital from the Opening of the Hospital in 1889 to July 1, 1906." Chapter XXIV, "The Cause of Uterine Myomata." Chapter XXV, "The Symptoms Associated with Uterine Myomata." Chapter XXVI, "Other Pathologic Conditions in Some of Our Myoma Cases." Chapter XXVII, "Differential Diagnosis." Chapter XXVIII, "The Effect of Removal of the Ovaries on Uterine Myomata." Chapter XXIX, "Abdominal Myomectomy." Chapter XXX, "Vaginal Myomectomy." Chapter XXXI, "Abdominal Hysteromyomectomy." Chapter XXXII, "Difficult Abdominal Hysterectomies." Chapter XXXIII, "Pregnancy and Uterine Myomata." Chapter XXXIV, "Complications following Abdominal Hysteromyomectomy." Chapter XXXV, "Results of Operations for Uterine Myomata."

Taken as a whole, the book is wonderfully clearly and interestingly written. It is essentially a huge case review with critical analyses. The authors have purposely left out all review of and practically all mention of the literature, stating in their preface that to do this efficiently would require the publication of a separate volume. The taking of this stand, while it renders the material more virile and interesting, has the disadvantage of not covering the subject absolutely. The authors, themselves, note that they have not done this in the chapter on myoma and pregnancy.

There are remarkably few typographical mistakes in the work; I notice, however, on p. 528, l. 10, that the word, puerperium, is used where pregnancy is meant; and in numerous places instead of the word, museauforceps, the word, mesoforceps, is employed. Likewise in the chapter headings the singular is sometimes employed and sometimes the pleural; in Chapter III, "Cervical Myomata," and in Chapter IV, "Submucous Myomata," while in Chapter XI we have "Angiomyoma" and in Chapter XIII, "Adenomyoma." It would seem that it would be clearer either to use the singular or the pleural uniformly. In the indexing of the book there are also certain awkwardnesses. For example, the reviewer wished to find out what the authors had to say regarding the possibility of conception in myomatous patients. He could find no reference under either pregnancy or conception but found that the matter was treated in the book on p. 475 and was indexed under "Fertility of Women who Develop Uterine Myomata."

The index likewise does not point to the page which shows what the authors have to advise regarding treatment of myoma in pregnancy. The general plan of the book is logical and excellent; we believe, however, that the chapter on adenomyoma is too brief. This important subject has been treated in three pages, a fact due to the recent publication by one of the authors of a large monograph on Adeno-Myomata. We feel that at least twenty pages should have been given to this subject in order to properly balance the book.

In the chapter on parasitic myomata the question of ascites is dealt with in a novel way; and in reading through the chapter on symptoms and diagnosis one gets quite new ideas regarding the occurrence and cause of hemorrhage in these cases. Especially commendable and original is the chapter on myosarcoma, which brings this subject into a light never before thrown upon it. This review, already too long, cannot go into further detail, but the reviewer recommends the work heartily to those interested in the subject.

The faults of the book are few compared to its virtues. It is a work which should appeal to several classes of readers. In the first place, it is easily the best laboratory guide to the normal and pathological conditions of myomatous uteri that has ever been published and should be owned by every worker in this field. In the second place, it gives in clear and candid fashion a great surgical experience which cannot but be of great interest and technical value to gynecologists and surgeons dealing with uterine conditions. And finally, the style is so attractive that the general practitioner can profit by the perusal almost as much as the specialist. The authors deserve and will receive great credit for the energy, originality and patience displayed in producing this work.

Sprains and Allied Injuries of Joints. By R. H. Anglin Whitelock, M. D., F. R. C. S., etc. (*London: Henry Frowde and Hodder & Stoughton, 1909.*) *Oxford Medical Publications.*

Dr. Whitelock's book on Sprains and the Allied Injuries of Joints, published by the Oxford University Press, is to be highly commended to the profession as a most useful work, supplying a very definite need. It is concise, clearly written and well illustrated. While its apparent brevity makes it more attractive to read, it contains sufficient detail on certain important points to make it a most valuable hand book to the general practitioner.

The author denounces with the force begotten of his great experience the treatment of every joint injury by the "rule of thumb methods" of indiscriminate massage or stupid incarceration in plaster, without first taking every means of finding out whether the injury is a simple sprain or one complicated by fracture. The one way of putting the diagnosis beyond a doubt, which may have such a serious effect on the outcome of the case, he declares, is resort to the "X-ray."

The two principal lines of treatment used in joint therapeutics, massage and passive movements on the one hand, and prolonged immobilization on the other, are discussed to great advantage with their uses and abuses. The bone-setter who treats every thing by rubbing and passive motion, will no doubt correspond more or less closely to our osteopath; while the more conservative, and perhaps more conscientious regular practitioner who treats everything about a joint with splints and plaster, also finds his analogue on this side of the ocean.

Dr. Whitelock shows where they are both wrong and that one may do as much harm as the other, if the treatment does not happen to fit the individual case.

Under no conditions is prolonged immobilization recommended, and the author lays emphasis on the muscular atrophy and the formation of fibrous adhesions within the joint which result from such treatment. Even when a sprain is complicated by fracture, he points out that early voluntary movements should be encouraged, as the nutrition of the joint and the muscles acting on it, is improved more by direct nervous stimulation than even by passive movements and massage.

Chapters 5 and 6 devoted entirely to the knee joint, are particularly interesting and instructive, being compiled from the study of a long series of cases subjected to careful observation. The poor results obtained by those who use the expectant treatment of immobilization are clearly pointed out. The author's method of treating the joint subsequent to arthrotomy, by drainage for 24 hours, is of such evident advantage in his hands, for the relief of fever and discomfort, that it is difficult to understand how any surgeon could fail to approve of it. Yet many surgeons of skill and reputation do not drain the healthy knee joint after operation.

On page 225 of the appendix, Fig. 63 represents an ankle strapped by the author's method. From the illustration it would appear that the adhesive plaster was carried entirely over the dorsum of the foot and around the ankle. The reviewer believes that it is difficult to strap an ankle in this way tight enough to give useful support, without producing a troublesome strangulation of the return flow of blood in the toes and anterior extremity of the foot. A narrow space left between the ends of the strapping, down the front of the ankle and foot, is all that is required to prevent this.

The book taken as a whole, while making no claim of adding materially to the sum total of knowledge on the subject, correlates, and puts in an attractive form, many important facts regarding joint injuries and their treatment, with some useful hints taken from the author's personal experience. J. S. D.

Operative Surgery for Students and Practitioners. By John J. McGrath, M. D., etc. Third Revised Edition. Illustrated. Price, $5. (*Philadelphia: F. A. Davis Company, 1909.*)

As the author states in his preface this edition differs from the two preceding largely in the section on abdominal surgery which "has been entirely rewritten." Those who have followed Dr. McGrath in his work at the New York Post-Graduate School will benefit by having an opportunity to learn what he considers the best abdominal technique, and others who read his surgery will find it a helpful book.

Duodenal Ulcer. By B. G. A. Moynihan, M. S. (Lond.), F. R. C. S., Leeds. Illustrated. Price, $4.00. (*Philadelphia and London: W. B. Saunders Company, 1910.*)

The author says the older writers described under the so-called "neuroses" and the term "dyspepsia" a great group of conditions which they believed to be chiefly functional, but which we now know to be due to organic diseases affecting not only the stomach but also the duodenum, gall-bladder or the appendix. He believes that among all these forms of organic disease, duodenal ulcer stands out clearest.

He says further, "we are now familiar with its symptoms, we have learnt of its dangers, and we are well-equipped with the means of treating it with permanently satisfactory results."

The work is based on the experience of the writer in the treatment of a large number of cases of duodenal ulcer, and he has, in addition, included the case reports of all published cases of Uræmic Ulcer of the Duodenum; Tuberculous Ulcer of the Duodenum, and Melæna Neonatorum and Duodenal Ulcer.

There are ten chapters as follows: History; Ulceration of the Duodenum in Cases of Burns or Scalds; Uræmic Ulcer of the Duodenum; Melæna Neonatorum and Duodenal Ulcer; Chronic Duodenal Ulcer, Symptoms and Diagnosis; Differential Diagnosis; Treatment of Chronic Duodenal Ulcer; Perforation; Pathology of Chronic Duodenal Ulcer; Appendix. Index of Authors; Index.

The appendix contains the details of all the cases operated on

by Mr. Moynihan to the end of 1908, and is written by Harold Collinson.

The illustrations are good, the book is well written and nicely gotten up.

The opinion of so eminent an authority, on a subject so familiar to him, makes the volume of great value. However, it is not always as easy to make a definite diagnosis of duodenal ulcer as the text might lead one to suppose. J. S. D.

Founders' Week Memorial Volume. Containing an Account of the Two Hundred and Twenty-fifth Anniversary of the Founding of the City of Philadelphia, and Histories of its Principal Scientific Institutions, Medical Colleges, Hospitals, etc. Edited by Frederick P. Henry, A. M., M. D. (*Philadelphia: Published by the City of Philadelphia, 1909.*)

This is an important and interesting volume, as it contains much information which could not be secured elsewhere or only with great difficulty and in scattered reports. As stated in the introduction it is not a complete history of all the scientific institutions of the city, but those represented are rather general than special. The histories of six are given: The American Philosophical Society; The College of Physicians of Philadelphia; The Academy of Natural Sciences of Philadelphia; The Franklin Institute; The Wagner Free Institute of Science of Philadelphia; and The Philadelphia Museums. Under the heading of Medical, Pharmaceutical, and Dental Colleges, the histories of nine are given. The Hospitals and Allied Institutions under Municipal Management are well described, and to this chapter Dr. A. C. Abbott has added an excellent paper on The Development of Public Health Work in Philadelphia. Twenty-six General Hospitals and Dispensaries; eighteen Special Hospitals and Dispensaries; and seven Asylums, Homes, and Training Schools, have had their histories carefully written. The volume closes with two chapters on Medical Societies and Medical Journals of Philadelphia. The work as a description of the medical life of the city is one of very great interest historically, and the editor is to be congratulated on the success of his undertaking, and the city authorities on their liberality in publishing it, a most worthy memorial of a city long famed for its medical work. It is abundantly illustrated and many of the pictures are rare and add largely to the value of the volume. As William Penn was practically the founder of the city it is to be regretted that his portrait is lacking.

BOOKS RECEIVED.

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Précis du Traitement des Fractures par le Massage et la Mobilisation. Par Dr. Just Lucas-Championnière. 1910. 12mo. 267 pages. G. Steinheil, Paris.

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Dislocations and Joint-Fractures. By Frederic J. Cotton, A. M., M. D. With 1201 illustrations; 830 from drawings by the author. 1910. 8vo. 654 pages. W. B. Saunders Company, Philadelphia and London.

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Transactions of the College of Physicians of Philadelphia. Third Series. Volume the Thirty-first. 1909. 8vo. 663 pages. Printed for the College, Philadelphia.

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Report of the Bombay Bacteriological Laboratory for the Year 1909. By Lieut.-Colonal W. B. Bannerman, M. D., D. Sc., I. M. S. 1910. Fol. 19 pages. Printed at the Government Central Press, Bombay.

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Dr McNeal

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CONTENTS.

THE SPECIAL FIELD OF NEUROLOGICAL SURGERY: FIVE YEARS LATER.[1]

By Harvey Cushing, M. D.,

Associate Professor of Surgery, The Johns Hopkins University, Baltimore.

The supreme misfortune is when theory outstrips performance.
—*Leonardo.*

Five years ago, at the instigation of my friend Dr. Crile, an address entitled "The Special Field of Neurological Surgery"[2] was read before the Cleveland Academy of Medicine, of which he was then the presiding officer. Advantage was taken of the occasion to make a brief explanation—to offer an *apologia,* as it were—for the contemplated restriction of my professional activities to what appeared at the time a narrow and unpromising field of surgical endeavor. Bearing this in remembrance, I have gladly accepted Dr. Chamberlain's invitation to address you again, for it seems a fitting opportunity to contrast with its former barrenness the relative fertility now shown in this small acreage, where seeds, though often planted in the past, have borne scant harvest from lack of intensive cultivation.

The reasons for this change involve certain principles of concentrated, specialized or intensive surgery to which I wish to allude at the outset. Among many of my surgical friends there exists, I am aware, a general tendency to disparage specialization; to minimize such services as have been rendered to the science as well as to the art of medicine by those who have particularized in gynecology, orthopædics, or genito-urinary surgery—to give some specific examples—or indeed in further subdivisions of these special fields. Perhaps we all should be "general surgeons," fitted by our comprehensive training to undertake anything in the way of an operation which the human body demands. But unfortunately this is impossible and such an attitude often entails consequences which are not only disastrous to the patient, but which also boomerang back unerringly to the ill repute of surgery, in the folds of whose mantle many overventuresome operators envelop themselves.

Though an occasional technical stride may be made through the operative courage of a McDowell, the permanent advances are far more often the result of patient laboratory investigations; such, for example, as led Hunter to ligation for aneurism, Bigelow to reduction at the hip, Billroth to intestinal anastomosis, Horsley to the first removal of a spinal cord tumor, Carrel to a perfected blood-vessel suture. The real leaders of to-day in surgery owe their place not to any special brilliancy in operative manipulations, but to their laborious experimental investigations of certain problems of disease, whereby has been disclosed a rational mechanical basis for a surgical therapy which can then be safely and successfully adapted by their many followers. Lasting contributions in surgery, as in any other field, are certain to come only as the result of such concentration. Without it, if we do not actually go backward or stand still, the advance at best is haphazard and spasmodic.

To the contributions of one group of intensive workers we

[1] An address, fragments of which were made to serve double duty before the alumni of the Lakeside Hospital, in Cleveland, January, 1910, and before the Cleveland Academy of Medicine, October, 1910. Printed simultaneously in the Cleveland Medical Journal.

[2] The Cleveland Med. Jour., January, 1905, and The Johns Hopkins Hosp. Bull., March, 1905.

owe the fact that extreme bony deformities are now a rarity, and that club-footed adults and the pitiful prototypes of Punch and Judy are no longer seen on every hand. The labors of others have made possible the amelioration and in many cases the certain cure of one of the most trying afflictions of advancing age—prostatic hypertrophy. To similar specialized investigations we owe nearly all of the striking and permanent advances which have come to be applied to the treatment of disease in their special fields by gynecologist, otologist, laryngologist, ophthalmologist, proctologist and the rest.[3]

Nor are we by any means at the end of specialization; for this tendency is merely a sign of the inevitable differentiation of work necessitated by advancing knowledge and the introduction of new methods. Who would have ventured, twenty years ago, to predict a special surgery of the blood vessels or of the thorax sufficient to engross the exclusive attention of productive workers. Forms of pressure apparatus promise to revolutionize the treatment of many intrathoracic lesions formerly inaccessible, and meanwhile the Roentgen ray and stereoscopic plates are threatening to supplant the stethoscope of Laennec in the early recognition of diseased foci, as they have already supplanted crepitation in the diagnosis of fractures. Meltzer's experiments even suggest a possible intratracheal treatment of lobar pneumonia. Then close on the heels of the successful suturing of the peripheral vessels doubtless will come a particular surgery of the heart and aorta: and though it is a long cry from John Hunter's experiments with the cock's comb to Carrel's visceral transplantations, it requires no wild imaginings to foresee the day of transplanted organs and members. It is obvious that clinical specialization in itself is no longer sufficient for the advances that are in the making; it must go hand in hand with laboratory experiences, as has been true of the work of Kocher, Halsted, Horsley, Crile, and other notable contemporary investigators.

But there is another element in addition to intensive effort which is essential to any notable advance in surgery—namely, opportunity, not only for the experimental or laboratory investigations, but for the clinical application of their results. Indeed, without it, well-directed efforts may be impossible. Unhappily it is common to see abundant opportunity lead to no concentration of work; but fortunately it is only rarely that special investigations go unrewarded by an opportunity to put the results into practice. This is true in spite of the widespread opposition to specialization on the part not only of individuals, but also of many institutions.[4] Too often, however, even when opportunity exists there may be wanting an inclination for research, which requires not only imagination but training; or what is too common, the inclination may be there and yet be blanketed by a deadly routine of institutional responsibilities. It is unquestionably essential to the productiveness of an investigator that he sacrifice all unrelated work to the immediate problem or problems at hand—and whether this sacrifice be justifiably continued for months or years or for the remainder of a professional lifetime, depends on the nature of the investigation and the character of the returns. Naturally a certain anxiety concerning livelihood lurks in the minds of all who are wage-earners rather than salaried individuals lest those dependent on us suffer through this sacrifice. But all such obstacles will never effectually deter from research one who has a natural bent in this direction, and the anxiety is assuredly a groundless one so far at least as surgery is concerned, for in this branch of medicine there are almost certain rewards for the contributor to knowledge.

But it is less of individual skill in this or that direction that I speak, for this is largely built upon experience: it is rather of the pathfinder's tendencies to enter new fields. One cannot blaze a new trail and continue on the old path at the same time: this is too much of a straddle for present-day surgery. The surgeon skilled in work on the alimentary canal and its appendages may set a broken leg abominably: and the orthopædist would often make a relatively poor showing in the treatment of a pyloric stricture. Nor should either attempt to do what he has either forgotten or has never learned.

Our rapid approach to a new order of things in medicine has been pointed out by many, and the fact must be faced, particularly by the present general surgeon and general practitioner, whose daily wage is noticeably shrinking through prevention of disease by school inspections, by boards of health, by campaigns for pure water and milk and against the "white" and "black" plagues, by district nursing, social service organizations and State hospitals for contagious and incurable diseases. The community is awaking not only to the better care for the sick, afforded by large and well-manned institutions, but to the possibilities of preventive medicine,

[3] There are large opportunities in our modern hospitals, among other surgical specialties, for a skilled proctologist who will investigate anew the common diseases of the lower bowel and finally contribute scientific procedures to take the place of our rule of thumb methods now applied to them. Important as its normal function is to the comfort and activity of mankind, the lower bowel has been abandoned as an object of special investigation for newer and less distasteful fields. Even the old saying that the chief reason for a surgical consultation is to have a rectal examination made no longer applies. Yet proctologists were among the first specialists. John Arderne, "master surgeon of the long robe," in the 14th century wrote an elaborate and much reprinted treatise on the homely subject of Fistula in Ano—a malady thought to be incurable before his time. In the treatment also he became expert, owing not only to his zeal, but also to unusual opportunity, for it is presumable that the long hours in the saddle of the heavily armored knights of his time, with the exposure and fatigue incident to the Hundred Years' War, was a frequent cause of this particular affliction. Again, four centuries later, though cures had become not infrequent, no less a one than Percival Pott deigned to write a special monograph, which passed into many editions, on this, surgically speaking, still important theme.

[4] The large general hospitals have been notably loath to recognize specialties, many of which have been forced to establish themselves at the outset in small institutions erected for the purpose.

and doubtless the great physicians of the future will more and more devote their energies to preventing disease in bulk rather than in treating it in the individual. In China the physician is paid only so long as his patients remain well, and on this basis modern methods of prevention insisted upon by a wise Government will some day enable him to double his livelihood. In this country, where doctors are paid, if at all, only for their attendance on the individual while ill, these methods, already being introduced, are having the contrary result.

But these coming changes are more apparent in their relation to the physician's than to the surgeon's activities, except in so far as the community is learning that surgical operations are necessarily safer in large hospitals, where the majority of them may come to be done in some future and more communistic time by salaried and possibly State-paid individuals who are specialists in their particular lines. For the performance of surgery is elaborate, expensive and time-consuming, and its more difficult forms, such as those which I am to discuss, must be carried out in familiar surroundings with a more or less fixed and permanent staff, so that the machine runs without hitch; otherwise safety will be sacrificed. The community deserves and, when enlightened, will demand better service than the old "cut and run" methods which still pervail in many, even of our larger, institutions.

The ideal surgical hospital would be one whose senior appointees after a broad general surgical training would be encouraged by continuous services to concentrate their work on special subjects—as many subjects as there are men who may be qualified as pathfinders. I realize, of course, that such positions cannot be created outright and men found to fit into them. Rather it will happen that positions must be built around such individuals as are available and must grow in accordance with the individual's capabilities. A junior staff in the meantime would carry on the general routine work, any subdivision of which, it is true, may become special to-morrow through some unexpected discovery, and again at some later day lapse back once more into the general mill, but always, it is to be hoped, on a higher plane.

A new department may any day be justified by an unexpected discovery which at the time may seem trifling. Chamberlen's forceps revolutionized obstetrics, the Wagner bone-flap made a new surgery of the brain, an "optical toy" of Helmholtz created ophthalmoscopy, Babington's mirror brought into being laryngoscopy, and otology received its impulse from the discovery of Eustachian catheterization. Thus not only may a demand for a new subdivision crop up at any moment, but the work of any established department may have to be entirely remodeled through a chance discovery—a new instrument of precision, a tissue stain, a serum reaction, a principle of vaccination. And the more of these discoveries there are, the more rapidly will the unfortunate and absurd segregation into two separate bodies, physicians and surgeons, be broken down. As simple a thing as the Pravaz syringe has made a surgeon of every physician who does a lumbar puncture, who aspirates the chest, or, indeed, gives a hypodermic injection: and were it not for this hollow surgical needle could we take a blood culture or administer Flexner's serum in meningitis? Physician or surgeon—it is really but a difference in the degree of surgical or medicinal dosage.[5]

But we continue to speak of "internal medicine" as though this were in contrast to "external medicine," or surgery. The surgeon before Lister almost of necessity was an "externist," but to-day the scalpel is the most satisfactory medicine for gallstones, for an inflamed appendix, a pyloric stenosis and much else internal. The tables are reversed, and the abdominal surgeon, strictly speaking, has become the "internist." Needless to say, then, he must share with the physician the same underlying knowledge of the function of the organs he treats and of the diseases to which they are liable, and must possess an equal diagnostic facility—indeed, he is likely to excel in this respect unless the physician makes a practice of frequenting the operating room.

This transformation of surgery from practices based almost wholly on an anatomical knowledge of the surface and extremities of the body, to ones based on the physiological activity of the viscera, has come rapidly, and physician and patient have both at times been hurt in the process. But it must be said of the physicians that their reluctance or hesitation to accept surgery as an oft-needed form of therapy, not only for the intra-abdominal maladies surrendered in the past, but for many intrathoracic and intracranial conditions of the present, has more often come through fear of surgical foolhardiness and its consequences than from jealousy of the surgeon's trade and ignorance of its possibilities in cautious and skilled hands. It is not to be questioned that the greatest asset of the best physicians is a full knowledge of the accomplishments of mechanical and operative therapeutics. The patients' risks are about equal between the physician who knows nothing of surgery and the surgeon who possesses no alternative but the knife.

It is all a matter of taste, what one shall do with himself in the wide reaches of Medicine. As John Locke puts it, "The inclination of the mind is as the palate to the stomach, that seldom digests well, that nauseates the palate, and is not recommended by it." So the turn of mind which breeds inclination for handicraft draws one into the manual work which repels another, but for all of us the fundamental need is a basic familiarity with the principles of disease, surmounted by such superstructures of special knowledge of a few particular maladies and their treatment as we are mentally and manually capable of imposing upon it. Thus any manipulative speciality may be safely superimposed on the secure foundations of general surgery and may exist with no loss of the broad conceptions of disease essential to its permanence: without such a foundation the specialty soon

[5] There is, of course, a certain danger in the too literal acceptance of Billroth's epigram, "Die innere Medizin müsse mehr chirurgisch werden," with which I closed my former paper. Surgery must beware lest it topple from its standard of general medicine. Surgeon and physician, standing on the same basis of common knowledge, differ only in the forms of therapy they are fitted by training or by inclination to employ.

becomes top-heavy, and the increasing numbers who are boosted by short cuts to the top increase its instability, until a danger sign is necessary lest the structure actually tumble to the ground and harm Medicine through its fall.

The present tendencies in gynecology serve as a familiar illustration. As the pioneers in this specialty pass, the feeling grows among their successors that the gynecological field has been worked out; and, widening the boundaries of their claim through this misapprehension, they unconsciously become again general surgeons—many of them, alas, with their general surgical knowledge built upon the sands of inexperience. Men with a broad surgical training first made this field possible as a surgical speciality, but others have occupied the territory without this preliminary schooling, and finding it, as they think, a very small field, branch out, spread themselves thin, and ceasing to contribute to its productiveness as a special field, become general surgeons of less than the average reliability. This is the top-heaviness to be avoided in specialization.

Gynecology, of course, as a special field of work has hardly been brushed, as doubtless will be evident some decades hence when the re-entry of new individuals on the old soil, with new methods, new machinery and a new spirit of investigation, will point a moral to our earlier selves. There has never been a day in surgery without those who have held that the highest attainment of the art has been reached, not only in general, but also in their particular fields.

This is the beginning of the end, I think, of all operative specialties. The specialty is the measure of the man. So long as there are individuals capable, after a general training, of working along novel lines and with the imagination for research which leads to contributions, so long will the field of their endeavors justify its being regarded as "special"; and it is almost impossible to make definite advances in one direction without permitting other work to go by the board. But so soon as progress lags and by the time others with no broad conceptions have crowded in, what was once specialization becomes properly absorbed again in general surgery, until perchance other pathfinders crop up whose work brings on a new cycle.[6]

In no department of Medicine to-day is there greater promise of immediate reward or greater need of intensive surgical cultivation than exists in neurology, which so far as the possibilities of operative therapy are concerned is about in the position occupied by gynecology twenty-five years ago—the days of tincture of iodine and the glycerine pack. There is urgent need and wide opportunity for a group of men rigorously trained in general surgery, in the neurological clinic and experimental laboratory, who can serve as pathfinders in the surgery of the central nervous system—men who are not merely capable of exposing the brain and spinal cord with full respect for the dire consequences of rough methods, but who stand abreast with the growing knowledge of the maladies to which these structures are heir. It must be obvious to all who peruse our numerous surgical text-books or converse on the subject with general surgeons, that the surgery of the brain and spinal cord means largely the surgery of their enveloping structures; and the methods of exposure—the getting in through the bony envelopes, by motors, burrs and what not, by the speediest osteoplastic methods and so on—is evidently the matter of paramount interest.

It is often appalling to find what disrespect is paid to the enclosed structures themselves as a consequence of this attitude. At a recent meeting, at which the subject of epilepsy was being discussed, a surgeon read a paper reporting twenty-five cases of epilepsy, with an astonishing percentage of "cures," and it came up in the course of the discussion that his method of treatment was "to sweep the index finger about between brain and dura" to be sure that there were no adhesions, and, in case there were evidences of tension, to insert the selfsame instrument in various directions into the brain substance "to be sure there was no tumor." Yet none of the neurologists present expostulated or showed astonishment!

In a recent consultation over a case of fracture dislocation of the spine resulting in an apparently total transverse lesion, which had been immediately operated upon without a preliminary, thorough neurological study, the area of anæsthesia corresponded to a level about three segments higher than the seat of the bony lesion—a level which could not possibly have been exposed by the incision which had been made. This finding was very confusing until it was learned that the operator, who with perfect skill and excellent technique had performed the laminectomy, had inserted his finger, at the close of the operation, into the canal "to be sure that there were no spicules of bone pressing on the cord higher up."

Such an appalling lack of respect for the most important and delicate structures of the body is doubtless far from uncommon. Instances could readily be multiplied. But the disrespect is not entirely confined to the surgeon, for the neurologist himself, having little familiarity with the hazards of surgery, may be responsible for the institution of measures as dangerous as those which the surgeon may undertake through lack of neurological knowledge. The recent suggestion, as a treatment for tabes, of peeling the pia-arachnoid from the back of the cord, as though this structure were a banana, is a case in point; and the indiscriminate puncture of the brain advocated by certain German neurologists in the

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[6] There are, to be sure, surgical specialties older than gynecology which have long existed, with none of these unsettling manifestations, though evidences of temporariness are by no means limited to the special gynecological field. Ophthalmology, obstetrics and orthopædics, for example, have remained stable. It is interesting that at Guy's Hospital there was no special department until 1824, a century after its foundation, when an ophthalmic clinic was created. An obstetric department followed in 1842, and one for laryngology and for orthopædics in 1885 and 1907 respectively. But no longer, as in the past, can the chair in any one of these clinics be held by the general practicing surgeon, for it has recently been decided that specialists alone are entitled to conduct the clinics for diseases of the ear, throat, genito-urinary organs and orthopædics, on the grounds that special training and skill are necessary. On such a basis special contributions toward the advancement of knowledge may be expected.

hope of finding a cyst or abscess, or of removing a small fragment from which a tumor diagnosis can be made, is a measure to be put in the same category, by no means excusable merely on the ground that the nature of the malady justifies blind and dangerous measures. "The condition cannot be made much worse, therefore operate," is a surgical dogma that should be squelched with its perpetrator. It is a sadly common excuse for much meddlesome and misdirected surgery.

Let us come, after this long preamble, to our special subject of neurological surgery, some aspects of which I have chosen for particular comment.

The Brain and its Envelopes.

Tumors.—At the time of my former paper the reaction from the discouraging views of Agnew and Bergmann had begun to set in, largely as the result of rumors of Sir Victor Horsley's brilliant undertakings in a large series of cases,[7] and of scattered records of occasional successful operations at other hands. Most neurologists, however, retain far from optimistic views. Nor can we wonder, when we consider the fact that Allen Starr, who with persistent courage has probably had more tumor operations done for him than any other, has recently reported what he regards as his first "cure" of a case of brain tumor—meaning not only the removal of the growth, but a complete restoration to the normal with disappearance of the signs, general and local, which made the diagnosis possible.[8]

Five years ago tumor cases were few and far between in the Johns Hopkins clinic, and though at that time there had been no successful extirpations, we had begun to feel somewhat encouraged regarding the beneficial effects of purposeful decompressive measures. A paper written on this subject[9] was quickly followed by the citation at other hands of numerous past cases in which trepanation had served to lessen preëxisting symptoms: the principle, in other words, was an old one. That relief of pressure in many instances had unexpectedly followed unsuccessful explorations for tumors had long been a matter of general knowledge, and Horsley, Weir and other forerunners in the work had been led to propose simple trepanation as an intentional palliative measure; but I am unaware that any author had previously suggested a purposeful decompression irrespective of possible tumor removal, and the utilization not only of a "silent" area, but also of overlying muscle to prevent too great protrusion of the herniating brain, or had ever emphasized the importance of decompressing at a distance from the growth as a preliminary measure should the brain prove to be under great tension.

However this may be, the decompression idea caught hold, and the frequent examples that have come under our observation of misdirected surgery, which results in making the patient worse, seem to have been born of an apparent misunderstanding of its most essential principles. Within the past few months we have seen two tragic examples of such errors. The patients, who had removable tumors in the left hemisphere, had been subjected to an exploration over the left central and precentral regions, with removal of bone and opening of the dura—a so-called decompression. In both cases the pressure symptoms had been largely relieved by the resultant hernia, but a complete motor aphasia and contralateral hemiplegia was the consequence in each case of the misdirected measure, leaving the patients in a most sorry plight.[10] Particularly when localizing symptoms suggest the presence of a growth in an important field of this kind, the greatest possible precaution must be taken to insure a sufficient reduction of pressure before opening the dura over the tense brain in the immediate locality of the lesion. This may necessitate two or three preliminary measures, as illustrated by the following recent case of suspected left prefrontal tumor:

A large bone-flap, so placed as to lay bare the anterior half of the left hemisphere, disclosed a dura so tight that it seemed inadvisable to lessen the tension by a lumbar puncture. Consequently a subtemporal decompression on this same side was combined[11] with the exploration, and the bone-flap was replaced after the dura had been opened merely over the silent temporal lobe. Though considerable improvement followed this palliative measure sufficient tension persisted to make a direct exploration hazardous; hence after a period of five days a right subtemporal decompression by the usual external intermuscular method was performed. Practically all the pressure symptoms subsided as a result of the bilateral subtemporal openings, and on the tenth day after the first exploration the bone-flap was again reflected, the dura was widely opened with only a slight degree of protrusion and a prefrontal tumor was disclosed and removed. This procedure was followed not only by abeyance of all pressure symptoms, but also by a rapid clearing up of the disorientation and intellectual disturbances which characterize lesions in this neighborhood.

A first-stage attempt to investigate the brain in this case would probably not only have resulted in failure to expose the growth, but doubtless would have led to symptoms comparable to those in the two cases cited. Thus in dealing with a tumor associated with extreme degrees of tension,[12] or with

[7] It is unfortunate that there is no published record of the ultimate results of his operations.

[8] Tumors of the acoustic nerve, their symptoms and surgical treatment. Am. J. M. Sc., April, 1910, CXXXIX, 551.

[9] The establishment of cerebral hernia as a decompressive measure for inaccessible brain tumors. Surg., Gynec. and Obst., 1905, I, 257.

[10] In one of the cases the tumor which actually proved to be largely post-Rolandic was removed, but the damage to the precentral cortex from the long-standing herniation was permanent.

[11] A method of combining exploration and decompression for cerebral tumors which prove to be inoperable. Tr. Am. Surg. Ass., 1909.

[12] It must be appreciated, too, that tension is always accentuated by a badly taken or poorly adminstered anæsthetic, and a second stage may be necessary owing to this factor alone. Expert anæsthesia, as cannot be too often emphasized, is a *sine qua non* in these procedures. Ether, too, possibly with a preliminary scopalamine or morphia and atropine injection remains the anæsthetic of choice, for reasons not apparent five years ago. In view of the inevitable hepatic necroses which follow chloriformization and the increased tendency to bleeding on its second administration, should one be necessary, the arguments in favor of anæsthesia by this drug in cranial operations have been greatly weakened.

a large and vascular growth, two, three or more stages may be essential to safety, however satisfactory it might be for all concerned if the lesion could be removed at the first sitting. It is needless to say that essential to the ultimate success of a performance necessitating the reopening of a large osteoplastic wound is the absolutely reactionless healing which alone is assured by a tedious, painstaking and accurate closure with early removal of the external approximating sutures.

We have had at this writing about 180 patients suffering from brain tumor, the larger number of them having been admitted during the past two years—namely sixty-four from October, 1908, to October, 1909, and nearly an equal number from October, 1909, to date. Some 250 operations[13] have been performed on these patients, including such preliminary measures as a subtemporal decompression for the relief of headache and preservation of vision before localization was possible.

Blind patients fortunately are brought to us less often than was the case a few years ago, and it would be interesting to compare the figures of the first fifty admissions in this respect with those of the last fifty. I should judge that they would be less than half as frequent in the latter.[14] Allowing a patient to become blind from the pressure of a tumor which does not directly implicate the optic paths is comparable to procrastination in appendicular disease until the onset of general peritonitis. The more or less satisfactory settling of the choked disc question has been in large measure responsible for this forward step, and ophthalmologists are now awake to the incipient grades of this lesion which previously were overlooked or, regarded as an "optic neuritis," were considered as something unrelated to pressure. Familiarity with the ophthalmoscope is an essential to this work and, thanks to the electric attachment, the old difficulties encountered in its acquirement have fortunately been greatly lessened.

For two or three years Dr. Bordley and I made repeated observations (daily in many cases) on the eye-grounds of the patients who were beginning to come to us in some number, and the conditions before and after decompression, not only in the tumor cases, but in other states of increased intracranial tension, soon convinced us of the essentially mechanical nature of the neuroretinal stasis and œdema. Similar studies have led Saenger, Hippel, Horsley, Paton, de Schweinitz, Schieck and others to similar conclusions.[15] An early grade of choked disc long remained the most delicate test which we possessed for the recognition of a tumor, and it was the custom to await its onset, for few ventured, five years ago, to make a diagnosis of tumor in the absence of headache and vomiting combined with choked disc.

In the course of our affiliated work routine perimetric observations were made of all suspected tumor cases before and after operation, and we found to our surprise that with great regularity a characteristic alteration occurs in the boundary relations of the color fields. This shows itself as an interlacing or actual inversion of the outlines of the color fields and seems to affect blue more than the other colors—a condition long regarded as typifying hysteria. The interlacing disappears promptly, as a rule, when sufficient relief from pressure has been brought about by surgical means; and what is of greater importance than all else, the condition is often demonstrable before there is any recognizable ophthalmoscopic alteration appreciable in the retina.

Six of our patients in the past year, in the total absence of a choked disc, have been subjected to operation largely on this basis; and some of our most satisfactory extirpations have been in this group. One patient had shown this change in the fields for over a year before we could bring ourselves to believe that he was carrying a tumor, for he had never had a headache, never any dizziness or gastric upset. Mild Jacksonian attacks starting in his left foot constituted the only symptom, and yet a benign tumor—an endothelioma weighing 200 grams—was found and removed, with complete recovery. This is the largest tumor in the series that was successfully removed: two larger ones, weighing 400 and 420 grams respectively, occurred in children who had long been thought to be hydrocephalic.

In only two out of about one hundred cases examined has all tendency to color inversion been totally absent. These were both cases of supposed cerebral arteriosclerosis with aphasia and focal epilepsy originating in the facial musculature. There were no pressure symptoms whatsoever in either case, but in each an exploration disclosed a small glioma in the lower precentral area. It is to be hoped, in spite of such exceptions, that the sign may nevertheless prove of value, for anything which will enable us to make an earlier diagnosis will be of untold benefit to these unfortunates.

Brain tumors are surprisingly frequent, and the diverse maladies for which the patients in our series had been treated for years, since many of these growths are slowly progressing affairs, would be a most distressing commentary on our diagnostic guesswork—the diagnoses, or shall we say guesses, ranging all the way from gastric headaches and eye-strain, arteriosclerosis, hysteria, neurasthenia and what not, to dementia, hydrocephalus and toxic amblyopia. Most common

[13] In these figures the first, second or third stage of a single procedure is not counted as a separate operation.

[14] I may, however, be too optimistic. At the present writing three patients from distant points have been admitted as follows: (1) A young man with a definitely localizable and approachable lesion had been subjected, until totally blind, to a rigorous antiluetic treatment for two years. (A temporal lobe cyst was found: he has recovered, though permanently blind.) (2) A respectable woman, needing decompression for an unlocalizable tumor and whose relatives had indignantly submitted for a year to an antisyphilitic regime, has become completely blind in the process. (3) A child of five years, having had mercurial inunctions for nine months, was brought, blind, hemiplegic and unconscious. (A large subcortical cyst—degenerated glioma?—was disclosed at a second-stage operation: the child has recovered, blind and hemiplegic.) The Wassermann reaction was negative in all of these patients: in none of them was syphilis remotely probable.

[15] Horsley's valuable paper ("Optic Neuritis," "Choked Disc" or "Papillœdema." British Med. Jour., March 5, 1910) should be consulted.

have been the diagnoses of functional disturbances insisted upon by the attendant until the pressure symptoms became full-blown, and then always the possiblity of syphilis had been considered, with an antiluetic regime, which either had added to the gastric distress and loss of weight, or, what was as bad, seemed to relieve symptoms for a time, leading to an erroneous diagnosis while the vision continued to fail. Fortunately the Wassermann or Noguchi reactions to-day make this diagnostic test by drugs no longer a matter which deserves discussion.[16]

They are ticklish performances, these operations for tumor, and demand not only a rigorous regard for detail, such as the patient's position on the table and the choice of the anæsthetic, coupled with the highest skill in its administration, but also a thorough knowledge of the diverse tricks of controlling hæmorrhage from scalp, meninges and brain, with a full understanding at the same time of the cerebrospinal fluid circulation under states of tension; for this latter is really one of the keynotes of success in these difficult problems, and upon the management of the fluid hinges not only most of the pressure phenomena which the disease elicits, but also the possibility of lowering tension during the operation in such way as to allow of dislocation and wide subdural exploration. The operation, in the hands of the inexperienced, must usually end with the first protrusion of the naked brain through an open dura, and when abandoned in this way, paralyses, a separated wound, an infected fungus, meningitis and death are, alas, too common. And it must be appreciated too that the management of the cerebrospinal fluid under these circumstances does not simply consist in its withdrawal by a lumbar puncture, for one of the most frequent causes of prompt fatality in patients suffering with tumor pressure is the wedged foraminal hernia which follows this ill-advised measure.

Our results, I am glad to say, are steadily improving with each block of cases, due doubtless to earlier diagnoses—for we now see proportionately fewer patients in the desperate terminal states of pressure—as well as to technical improvement in the various procedures, for barring such clean-cut lesions as those, for example, which constitute the group of lateral recess tumors, no two patients present exactly similar problems. In our last one hundred cases, over a period of eighteen months, there were eight operative fatalities in the first fifty and only three in the second fifty; there were only ten extirpations or six cyst evacuations with practical cures in the first fifty, and there have been twenty in the last fifty. In the entire one hundred, therefore, there have been thirty apparent (to all intents and purposes) cures, thirteen operative deaths and sixty-seven measures which have been definitely palliative. There has been a complete absence of the old-time post-operative complications. A meningitis or fungus cerebri is almost inexcusable to-day.[17] Some of the patients subjected merely to palliative measures have since died, some have been subsequently operated upon for tumor removal; but the majority continue well, many of them earning their livelihood. Brain tumors, be it known, are almost always slow-growing affairs, the more serious kind too—the gliomas—growths which tend to undergo degenerative processes, so that if not only room is made for them but time is also allowed they can be long carried without further symptoms provided they occupy silent areas; and this is the group of cases for which palliative measures are particularly indicated. It sounds like an Irishism to say that no tumor is so favorable for operation as one which cannot be localized, and yet it conveys much of truth.

Contrast these figures with the gloomy statistics built upon post mortem examinations, with only four per cent of tumor cases suitable for operation! It can be seen that there is enough surgical work among patients suffering from brain tumor alone for concentration—specialization within the field of neurological surgery. Without this specialization the work cannot be done well, for it is hardly a physical possibility to carry to a safe termination more than one of these arduous operations in a day, nor is it fair to the patient or to the subject we are discussing to undertake such work when fatigued or to crowd such operations into the midst of a busy day of general operative surgery. Then, too, hours of preliminary and of subsequent study are demanded by these conditions, as the neurologist well knows; and the neurological surgeon must look at his subject from the neurologist's standpoint and must make his own diagnoses, just as do the better men among those who are contributing to the surgical therapy of the diseases of the alimentary canal or genito-urinary tract or pelvic organs or ductless glands, as the case may be.

Headaches.—One by-product of the decompression idea which has aroused our interest has grown out of the striking relief from the intracranial discomforts experienced by patients with tumor, through the establishment of a subtemporal defect in bone and dura. This matter concerns those unfortunates who are constant sufferers from intractable migraine. There are many types, of course, of hemicrania and many causes for it, but in one familiar group there occurs during the attack a marked arterial dilatation of the temporal vessels accompanied by a venous congestion which is seen best in the external branches of the ophthalmic vein, but which is observable, too, by the ophthalmoscope in the eye-grounds. Ptosis, pupillary inequality, vomiting, slow pulse and other familiar symptoms, associated at times with a low grade of

[16] Confusion is often rendered worse confounded by the fact (1) that the pressure symptoms of a glioma may temporarily subside under mercury and iodide, and (2) that the fibrous gumma is notoriously resistant to these same measures. It is to be hoped that Ehrlich's new arsenical preparation will be as effective in the absorption of this form of syphiloma as it promises to be in the earlier lesions of the disease; thus obviating on the one hand the necessity of considering these cases as surgical and on the other of the protracted mercurial treatment of the present and past.

[17] Though it is our invariable rule to shave and cleanse the scalp on the operating table before anæsthesia, with no preliminary ward preparation, there has never been a wound infection, meningitis, or, even with the tense hernia which may form, a broken wound leading to a fungus cerebri.

choked disc, accompany the attacks, and a number of these individuals have submitted with eager willingness to the experiment of a subtemporal decompression, which has resulted in a considerable measure of relief in most of them. What encourages us to believe that the step is in the right direction is the fact that when subsequent headaches occur there is evidence of increased tension shown by a tendency to protrusion at the seat of the defect, which becomes flat again, or even recedes, with the free interval. The seizure would seem to be brought about by some local nerve discharge acting on the blood vessels and causing pressure from a circumscribed œdema, possibly of the nature of an angio-neurotic œdema. Nevertheless it must be admitted that the matter demands much longer study before it can be advocated on a sound basis of therapy.

Intracranial Hæmorrhages.—Possibly no one of the recent contributions to the surgery of the head has proved so simple or has been so satisfactory as the decompressive measure, whether unilateral or bilateral, as the case demands, for basal fractures. This procedure has become more or less routine in our clinic, and has been put upon such a basis that it may safely be regarded as a task for the general surgeon. The same, unfortunately, cannot be said as yet of the traumatic intracranial hæmorrhages of the newborn nor for the hæmorrhages consequent upon vascular disease in the adult.

Since my first paper suggesting intervention for birth hemorrhages,[18] in which four cases were reported, the opportunity has arisen to make similar attempts on twelve other infants, several of whom were in a desperate condition, extensive contusion of the brain being associated with lacerations of its enclosing structures. About half of these patients succumbed during or soon after the operation, but some made excellent recoveries without the dreaded spastic paraplegias which Little was the first to ascribe to these accidents of birth. The second of the cases described in my original report is now a healthy and normal child of five years of age. Unfortunately I have lost track of the third child, which also made an immediate surgical recovery. Several of the later patients have also done remarkably well, though in one or two of them, doubtless due to complicating extravasations in the basal ganglia, athetoid states have supervened. The surgical procedure is usually well borne, which is not suprising when we consider the inevitable trauma which nature has fitted the child's head to endure successfully even at a normal birth. But the procedure is a delicate and difficult one, and until much more can be learned regarding the late results and the best methods of procedure I do not feel that it can be widely advocated for general use.

The same applies also to the question of apoplexy. I feel that much of the damage which occurs in these conditions is due to compression from the extravasation and to secondary œdema rather than to actual destruction of important nerve-paths—an explanation which also applies to the paralytic symptoms of tumor cases—and it would seem rational, if we are to regard patients with cerebral vascular disease as deserving of such radical measures for their relief, to attempt the removal of the clot, even though it be intracerebral, just as we would were we dealing with an extracerebral extravasation. A note was made some seven years ago[19] in a Mütter lecture of our first attempts in this direction, and since then there have been possibly a dozen cases operated upon, most of them in the terminal stages of compression. There have been one or two excellent recoveries, but whether they would have been equally satisfactory without the operation must remain a matter of some uncertainty until a much larger group of cases has been studied and a much longer interval has elapsed. Our attention has been drawn into other fields, but I feel that any one who would devote himself to this particular subject might hope for valuable results.

Hydrocephalus.—Possibly no condition is looked upon with a more general feeling of helplessness than infantile hydrocephalus, with or without the frequently combined spinal defect. That we shall some day find a rational method of surgical treatment for these cases I have not the least doubt, but it is very unlikely that it will come from indiscriminate attempts at drainage, for which some thirty different methods have already been advocated. The underlying factor of cerebrospinal fluid circulation must first be worked out, for it is this which is at fault; and whether there is an excessive activity on the part of the choroid plexuses or whether there occurs an obstruction at some stage between the plexus and the points of exit of the fluid from the cranial chamber, is not entirely clear.

Though we are learning much in regard to the acquired forms of hydrocephalus due to obvious obstructions, the "essential" or "idiopathic" hydrocephalus—so-called because we have never thus far been able to solve its mysteries—is still most baffling. Its elucidation will only come, I am sure, to the one who clears up the development of the ependymal and meningeal spaces and who can show us the normal outlets of escape from the arachnoid. That the fluid is constantly being formed, that its main normal escape is from the subarachnoid space into the dural veins and sinuses, that it has a close association with the venous rather than with the lymphatic system, that it is a carrier of secretion elaborated by the posterior lobe of the hypophysis, that in most of these cases of "essential" hydrocephalus the fluid actually finds its way from the ventricles into the subarachnoid spaces, so that the former can be emptied by a lumbar puncture, making absurd most of the advocated methods of drainage—all this and more has been learned. Moreover, it is a well-recognized fact that hydrocephalus—since it is only a symptom of disease and not a disease in itself—is found in a great variety of pathological conditions, each of which will demand its particular form of readjustment to assure the proper fluid drainage. I hesitate to say how many harrowed parents apply for surgical relief for hydrocephalic offspring,

[18] Concerning surgical intervention for the intracranial hæmorrhage of the newborn. Am. J. M. Sc., October, 1905.

[19] The blood-pressure reaction of acute cerebral compression, illustrated by cases of intracranial hæmorrhage. Am. J. M. Sc., June, 1903.

or how many of the cases have been operated upon, or how discouraging have been most of the results. Of one thing I am convinced, that we are only at the threshold of this subject and that it is large enough to need its own specialization.

Epilepsy.—Here, again, we are dealing with a symptom of disease, for the use of the term "idiopathic" or "essential" is again an acknowledgment of our ignorance of the etiology. Hence in speaking of the surgical treatment of epilepsy we must not overlook the fact that in an ever-growing number of cases we are dealing with convulsions of recognizable organic origin, be the cortical irritant a tumor or a cyst, local vascular disease, the relic of an old inflammatory process, or a gliosis set up at the seat of an old traumatic extravasation however minute.

With Dr. Heuer, I have gone through our voluminous tumor histories with the object of determining the number of patients in this particular group who have suffered from seizures of an epileptiform character. In 130 consecutive cases, convulsions were recorded in 53 (40.7 per cent), and of these patients, 27 had typical motor Jacksonian attacks—practically the only symptom of tumor in a certain number of them, so that, as Allen Starr emphasized many years ago, these cases should always be explored on the suspicion that a cortical new growth in a removable stage may be responsible for the symptom. This in the past has applied only to paracentral lesions with motor fits; but now it is possible, thanks again to Hughlings Jackson, to recognize some forms of seizure which have originated from cortical lesions elsewhere—the uncinate gyrus group of fits, for example, of which nine instances have occurred in our series. It must be realized that a lesion identical with that which evokes a characteristic Jacksonian attack when in proximity to the motor cortex, may, when situated elsewhere, elicit what appears to be a general convulsion without warning.

A lesson is to be drawn from the experience with these tumor epilepsics; namely, that the attacks, if they have been of long standing, may continue even though the growth, obviously their original cause, has been cleanly and totally removed. There is a certain basis, therefore, for the common idea of the "establishment of an epileptic habit," which means nothing more than that certain fixed alterations occur in the cortical cells which make them more liable than formerly to discharge under a certain stimulus—whether chemical through autointoxication, or mechanical from varying degrees of intracranial tension, or vascular through blood-pressure changes. This point furnishes one further inducement to precocious explorations in incipient epilepsy whenever there exists an element of suspicion that a focal lesion due to an original trauma or infection is present.

In Keen's system of surgery two years ago I summarized the fifty-nine cases of general epilepsy which I had operated upon up to that time, and stated that 50 per cent of the patients had been so far benefited, temporarily or permanently, as to make the operation seem worth while. We have had almost as many more cases during the past two years showing proportionately about the same degree of benefit. Just why these patients should have such a marked subjective sense of relief and so frequently a complete cessation of seizures for a time, I can offer no satisfactory explanation. In a small number of cases the operation has apparently resulted in a cure with complete abeyance of the attacks for a number of years, and this too not infrequently in cases which appeared to offer the most unpromising surgical risks: whereas on the other hand, many of those which, surgically speaking, were most promising have relapsed again practically into their former state.

There are many factors to be considered in an analysis of these cases, such as the preëxisting duration of the malady, the number, severity and character of the attacks, the after-treatment and environment, the lesion found at the operation and the procedure employed—extirpation, arachnoid drainage, ventricular puncture, decompression or what not—too many factors, indeed, to justify an analysis in a general address.

Dyspituitarism.—Hidden in a foot-note in the paper of five years ago I find this statement, "It is not impossible that a diseased pituitary body may some day be successfully attacked"—probably, I meant, in the next generation. To Kipling's story of the "Night Mail" there are appended fictitious advertisements of flying machines and their accessories culled from presumptive newspapers of the year 2000. An energetic house in England in advertising their present sale of such articles has called attention to the fact that according to Mr. Kipling they are ninety years ahead of time. It would require the imagination of a medical Victor Hugo to forecast what the surgical activities even of the immediate future may be.[20]

But much more important than the mere happening of certain successful operations for the treatment of lesions in the infundibular region which have implicated the pituitary body, is the greater fact that through these efforts and the associated experimental work, diseases hitherto mysterious are beginning to be understood. Surgery here can occupy the same rôle that it played in the diseases of the thyroid gland. But surgeons should eagerly acknowledge their debt to a neurologist—Marie—who was the first to point out the association of a pituitary body lesion with a definite clinical syndrome, and to other neurologists who have led the way in throwing further light—so far as light can be thrown by clinical investigation alone—on other and correlated maladies of hypophyseal origin. Furthermore, from an anatomical point of view the hypophysis is an intracranial structure—the "brain gland" of our forebears—and doubtless its normal secretory relationship to the cerebrospinal fluid makes the gland in a way as important to neurology as its membership in the family of ductless glands renders it of importance to general medicine.

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[20] The suggestive papers of Marburg and of Pappenheim (Virchow's Archiv, 1910) indicate that the pineal gland is deserving of special experimental investigation and may prove to have an importance to the economy other than as a vestigial seat of the soul.

Our brethren, the rhinologists, I am told, wish to take this structure unto themselves as a partial denizen of the nose, and doubtless they can find their operative way to it as readily as can any others. But no matter who takes the lead and by further investigation advances our knowledge of this fascinating structure, let the clinical applications come primarily and exclusively as the result of serious experimental research, not as the chance experience of an isolated case or two of hypophyseal cyst or tumor operated upon by a single individual. Such sparring for a small prize temporarily blackens the eye of surgery, for, though he may not know it, conservative surgery is the natural opponent of the casual operator. Such was the story of brain tumors in the eighties. The men who are making aerial flight a thing of the near future are not the "spellbinders," thrilling as their individual flights may be, but the men who, like Langley and the Wrights, are working at principles.

The hypophysis and the ductless glands in general so influence the function of every organic process that they overlap into every individual specialty, and it is a free-for-all race, but one beset with so many obstacles that progress toward the goal will be slow. Newton once likened the sons of men to children, who on the beach of knowledge pick up a pebble here and there, while the wide ocean of the unknown lies stretched before them. We shall doubtless have to drain it to its dregs before all the pebbles relating to any single subject will be disclosed.

It has been learned that the anterior lobe of the gland is essential to life, and that it bears a close relation to such disturbances of growth as are displayed in gigantism, acromegaly and certain forms of infantilism. The infundibular lobe, on the other hand, is closely bound up with metabolic processes, and in view of the discovery that its secretory products are present in the cerebrospinal fluid this pars posterior must take on a new importance in many morbid states closely related to the nervous system.[21]

Surgically speaking, despite the demonstration that the sella turcica is accessible, we are still working in a dim light, and the proven importance to life of the glandular structure which rides in the saddle must breed hesitation in the minds of those who would dislodge it offhand. As yet the surgical problems should properly be restricted to the relief of neighborhood symptoms brought about by new growths which have either originated in the gland itself or have arisen from adjoining structures. No one as yet would venture to assert that a tumor in the infundibular region can be totally removed, and inasmuch as pituitary headaches and pressure against the chiasm may be relieved by a local decompression or by the chance evacuation of a cyst, it would seem wise, for the present at least, in view of the importance of the gland, to confine operative measures in most cases to the mere removal of the sellar base with incision of the glandular capsule —a local decompression. Hypophyseal tumors which have extended from the infundibular region into the cranial chamber proper must be treated by the same rules of cerebral decompression as would be applied to any equally inaccessible lesion elsewhere.

An attempt will soon be made to correlate the clinical studies of our 20 cases of hypophyseal disease in man, with the experimental observations conducted in the Hunterian laboratory by Reford, Crowe, Homans, Goetsch, Dandy and Jacobson. Symptoms due to a primary or neighborhood disease are often more or less obvious, but those due to a secondary implication of the glandular activity from a lesion elsewhere are a far more common sequence of intracranial maladies than is generally supposed.[22]

The Spinal Cord.

Meningitis.—Far less that is new has been added during these five years to our manipulative therapy of lesions of the cord than of those of the brain. The temptation is to dwell on Flexner's remarkable achievements rather than on matters surgical, for his past work has resulted in the prevention of many of the surgical complications formerly a consequence of meningitis and his present investigations on poliomyelitis when carried to the end may have an even more striking tendency in this same direction. There are some sequels of cerebrospinal fever, however, which present surgical problems during the course of serum treatment or even when recovery has been brought about by its use.

It has been pointed out that all of the fatal cases die with, if not in consequence of, an obstructive hydrocephalus,[23] so that intraventricular as well as the usual lumbar subarachnoid introduction of serum may be indicated. Indeed, in one of our cases, when organisms were no longer demonstrable in the spinal fluid, they were present in abundance in the distended cerebral ventricles. It is possible, therefore, that drainage of the ventricles (temporarily to the outer world, or permanently to the subdural space by the ingenious callosal puncture method, introduced by von Bramann[24]) may be therapeutically applicable to this frequent complication. Then there are certain late disturbances which may supervene after apparent recovery—epilepsy, for example, and spinal paraplegia, both presenting problems for operative treatment.

[21] Concerning the Secretion of the Infundibular Lobe of the Pituitary Body and its Presence in the Cerebrospinal Fluid. Am. Journ. of Physiol., November, 1910.

[22] A note of caution in regard to the therapeutic use of hypophyseal extracts may not be untimely—particularly as their employment is being recommended for certain surgical states. Operators grasp eagerly for any blood-pressure raising substance which can be employed in shock, as was disastrously the case with adrenalin. Pituitary body extracts which are "on the market" advertise to the unsuspecting that they occasion a more marked and more enduring rise in arterial pressure than adrenalin. Unfortunately the gland appears to contain two substances, one of which produces as marked a depressor as the other does a pressor response, and until they can be separated, therapeutic administration in cases of low blood pressure might prove most dangerous.

[23] Obstructive hydrocephalus following cerebrospinal meningitis. J. Exper. M., 1908, X, p. 548.

[24] Bewerthung des Balkenstichs in der Hirnchirurgie. Arch. f. klin. Chir., 1909, XC, Nr. 3.

Some of our best results in epilepsy have been obtained in this group of cases, and a number of patients in whom a progressing spinal paraplegia had developed, have been much benefited by a laminectomy. In some of the patients who suffered with severe pain the posterior roots have been divided, and in all of them the chronic adhesive arachnoiditis, often with so-called serous cysts, has lent itself to surgical betterment. Into this same category fall the cases which have been given the sonorous name of "arachnitis adhesiva spinalis circumscripta." Oppenheim, Krause and Horsley, among others, have called particular attention to these encysted accumulations of fluid in the arachnoidal spaces which may cause pressure disturbances akin to those associated with a new growth; and doubtless all who have performed many laminectomies for a presumed tumor syndrome have had the good fortune to encounter this condition, which lends itself favorably to operative treatment.

The acute tuberculous and pyogenic infections still waver on the borderline of surgery. It is remarkable that a tuberculous meningitis, regarded as inevitably fatal, should show so little for itself after death, for one must often scrutinize the meninges for the presence of tubercles even though the bacilli have been demonstrable in the cerebrospinal fluid during life. On the assumption that a supervening serous meningitis has been responsible for these fatalties we have drained the mid-subarachnoid cistern through a median occipito-spinal opening—an operation easily performed—with obvious temporary improvement, which, however, merely served to postpone the seemingly inevitable outcome. It is possible that a callosal perforation may here again be applicable, for a hydrops ventriculorum tends to form in these cases just as it does in the course of the meningococcus infections.

Much better results have been obtained from permanent drainage in the cases of serous (non-tuberculous) meningitis and in those of pyogenic origin. A number of patients suffering from an established general streptococcal or pneumococcal infection have recovered after the establishment of free drainage coupled with the administration of urotropin. One could wish that Crowe's discovery,[25] that this drug quickly finds its way into the cerebrospinal fluid, might be applied to cerebrospinal fever as an adjunct to the serum treatment. There is no doubt, however, that its chief value will be as a prophylactic measure in conditions such as otitis media or sinusitis or basal fractures in which meningeal infections are threatened. On this basis it might well deserve a vigorous trial during the only too brief prodromal stage of acute poliomyelitis, or be used as a general prophylactic in localities where the disease is epidemic, as quinine is employed in malarial districts.

Tumor.—We have had a number of cases of spinal tumor, and possibly there is no performance in surgery more interesting and satisfactory than the diagnosis and localization, followed by the removal from the spinal canal of one of the benign meningeal endotheliomata. The subsequent relief from excessive pain and the resurrection from crippledom of one of these unfortunates are chief among the things which make for optimism in neurological surgery. It is astonishing how great a degree of recuperation exists in some of these flattened cords. In one of the cases in our series of six—a woman with total paraplegia of two years' standing—the cord was found thinned to a flat band of a few millimeters, and yet she has regained almost complete control of the extremities and walks freely without crutches.

The principle of decompression, furthermore, is often as applicable to the intramedullary tumors of the spinal cord as it is to the subcortical tumors of the brain. Among a number of cases of this sort the following may be cited as a notable instance of improvement after spinal decompression:

A young woman whose symptomatic history was confused by an early poliomyelitis followed by an extreme rotary curvature of the spine, began to lose control of her legs and visceral reflexes, until the lower body was almost totally paralyzed. There were no root pains, but she suffered from severe suboccipital headaches, and the diagnosis was obscure. A long S-shaped laminectomy disclosed a tense, pale cord which, filling the canal to the complete exclusion of fluid, bulged outward through the dural opening. A longitudinal incision in one of the posterior columns revealed a columnar glioma, a portion of which was removed for diagnosis, and the laminectomy was further enlarged upward until it included eight vertebræ before the upper limit of the extreme spinal distension seemed to be reached. There were almost immediate signs of returning function, motor and sensory, and she has so far recovered as to make us regret that the posterior column was not slit throughout the entire length of the exposed and tense cord. It is possible that such a neoplasm may degenerate, as in the case of some of the cerebral gliomata, into a cystic lesion of syringomyelic nature.

There is another form of palliation which may save from much suffering those unfortunates who have a malignant (metastatic) involvement of the cord which is beyond surgical attack—namely, the deliberate transection either of the entire cord or of the posterior columns alone, cephalad to the lesion. An immediate suprapubic drainage will suffice to keep these pitiable individuals clean, and they may be spared months of pain of such a nature and of such severity, under the usual circumstances, as to so far prohibit movements of the body that bed-sores develop even under the best of care.

Trauma.—In view of the recoverability of function in cords flattened by the pressure of tumors, one might argue in favor of equally satisfactory results in the case of traumatic injuries. This, alas, does not follow. On the one hand the slow compression effect leads to a physiological "block" to the transmission of impulses, which, however, is rarely if ever functionally total, the reflexes usually being retained while the paraplegia is of a spastic type in which spasmodic and uncontrollable movements occur. On the other hand there has been a laceration of the cord with an anatomical division of the conducting paths which makes a lesion beyond repair, and transection itself permanently abolishes the deep reflexes and gives a flaccid paraplegia.

I do not feel that on operative grounds I have anything to add to the subdivision of traumatic spinal injuries into three

[25] The excretion of hexamethylenamine in the cerebrospinal fluid. Johns Hopkins Hosp. Bull., 1909, XX, p. 102.

groups as made five years age—the hæmatomyelias, the total transections and the partial transections. The first—an easily recognizable condition—should not be operated upon, as it is in large measure a recoverable lesion, which cannot be bettered by surgery and may be made worse. The second, if it can be recognized without qualification, should not be meddled with, as the condition is hopeless beyond repair with or without surgical intervention. The third may and should be operated upon as soon as the diagnosis is made, provided the operator's experience is such as to insure no further damage to the cord in the effort to free it from pressure and relieve it from the effects of a progressive œdema.

It is possible that we cannot rely as definitely as Bastian would have had us believe, on the permanent as well as immediate abolition of the deep reflexes in cases of total transection, for there have been a number of cases recorded of total cross lesions (proven to be such post mortem) in the cervical region in which deep reflexes have returned; and I have seen two or three striking instances of similar restoration in cases which presented all the signs of totality immediately after the injury. One cannot, therefore, speak at all times with positiveness in regard to totality of transection, and final judgment on the individual problem must needs be influenced by associated circumstances. One can, however, do much for the cleanliness and comfort even of these desperate cases; and an early suprapubic cystostomy with the snug insertion of a tube through a small, widely stretched opening will usually avoid the renal infection which under repeated catheterization was formerly inevitable. Urethral drainage is far less effective. Fortunately these cripples rarely suffer physical discomfort and life may be tolerable and hopeful.

Something may be said as to operative methods in laminectomy, for an entry accompanied by rough manipulations is just as much to be condemned here as in operations on the brain. A temporary increase of preëxisting palsies is an evidence of operative traumatism, not to be excused on the basis of œdema or otherwise laid at nature's or the patient's door. The proposed osteoplastic operations are assuredly inadvisable, and I adhere strongly to the old total removal of spines and laminæ. The operation is actually a very bloodless one if the incision is absolutely median and the spines and laminæ are closely hugged and scraped of their periosteum. With this precaution new bony arches may almost totally reform, as we have had occasion to learn in a number of cases with secondary exposures, and the column seems to be weakened in no respect, even after an extensive removal. In one patient, during the course of three investigations for a presumed tumor, although all laminæ have been removed from the first thoracic to the second lumbar inclusive, his back is strong and no mechanical support is required.

Rather than saw through the laminæ or chip them off with gigantic forceps I prefer, after removing the spines, to enter the canal with a perforator and large burr, introduced successively at the amputated base of each spine. The lateral fragments of the laminæ can then be nibbled away with sharp-nosed rongeurs. This method of entry not only spares the operator's reflexes for the delicate work to follow, but avoids all jar to the cord. After the median extradural fat has been scraped from the dura this membrane should be incised on a director with such care as not to injure the subjacent arachnoid which bulges into the wound and through which, under normal circumstances, the contained structures can be beautifully seen as if magnified through a glass. If a looked-for tumor is not exposed a delicate filiform catheter may be readily passed upward between the dura and uninjured arachnoid as high as the foramen magnum, if there is no obstruction in the canal such as would be produced by a growth. The preservation of the arachnoid and its contained fluid is desirable as an immediate aid for these primary explorations, but not for the reason that evacuation of the fluid is dangerous. We at least have never seen any untoward symptoms result from its complete outflow so long as the patient's head is not elevated; and I am inclined to ascribe the oft-mentioned "spinal shock" to the loss of blood and trauma incidental to rough methods of entry rather than to escape of fluid. These spinal wounds of course should never be drained.[26]

The Peripheral Nerves.

The surgery of the peripheral nervous system, at least so far as the nerves in their extracranial and extraspinal course are concerned, has long been a field of "external surgery," and much of our knowledge of the effects of injury and recoverability after suture dates from the past century, which has also brought down to us the tradition of perverseness which makes nerves reunite when this is undesirable and prohibits functional union when it is longed for.

Harrison's remarkable studies which were in progress at the time of my earlier paper, have since added further knowledge to the question of possible peripheral auto-regeneration which was then exciting much discussion. By the further aid of experimental surgery on embryos he has succeeded in bringing the living fiber under direct observation[27] during its early formation. The nerve fiber develops primarily as an outflow of protoplasm from its central cell, the end of the fiber showing a filamentous structure possessing motile characteristics which draw out the protoplasmic thread into its permanent axonal form, no other cells taking part in the process. This amœboid property doubtless appertains to the regenerating central end of the divided adult fiber and is doubtless what leads to reunion of a severed nerve in the adult; the sheath of Schwann cells of the peripheral segment possibly playing some chemotactic rôle, as experiments have suggested, in attracting the axone toward its old path, but certainly taking no direct part in the reformation of a sep-

[26] An ingenious unilateral laminectomy has been introduced by Alfred S. Taylor, with which I have had no experience but which I should judge would leave too narrow a defect in the column for any manipulations within the canal other than the simple root divisions, for which purpose I understand the operation was devised.

[27] Observations on the living, developing nerve fiber. Anat. Record, 1907, VII, p. 116.

arate peripheral axonal segment. Harrison has also shown that in certain frog larvæ there may be such a thing as primary protoplasmic union of axis cylinders without degeneration. Studies such as these make far clearer our working conceptions of the processes of reunion of old or newly divided peripheral segments with their original, or, after grafting, with new central ends. The delicate amœboid end of the newly growing axone cannot well respond to the peripheral call when an abundance of scar tissue is interposed, particularly when the tendency to its formation is augmented by the presence of bulky silk sutures. Experimental studies, however, have not as yet shown why it is that sensory fibers show a much greater tendency to reunite than motor fibers. If the reverse were true, much of our peripheral nerve surgery would be rendered easier.

Important additions to our knowledge of the afferent system have come from the exhaustive clinical researches undertaken by Henry Head [28] and his co-workers, Rivers, Sherren and Thompson. A painstaking investigation of a long series of nerve injuries which culminated in the subjective studies of the anæsthetic skin-field produced by purposeful severance of the superficial ramus of the radial in Head's own arm, led these authors to subdivide the sensory mechanism into three systems, which convey impulses of (1) deep sensibility, (2) protopathic sensibility, and (3) epicritic sensibility. These studies have shed a new light on certain factors relating to sensory restoration which have long puzzled surgeons and which have either been explained on the basis of overlapping or at times entirely misinterpreted as an immediate return of function after suture. The "protopathic" system of Head regenerates with rapidity and completeness, even when the true cutaneous supply ("epicritic") remains cut off, and he regards it as one with the afferent fibers of the visceral sympathetic. This particular system is incapable of appreciating touch and slight degrees of warmth and cold; all stimuli are imperfectly localized, radiate widely and are often referred to distant parts as painful impressions. Their detailed and systematic investigations of about sixty cases of nerve injury have not only given us many important new facts, but have set a standard of thoroughness which can be attained by few others.[29]

Nerve Anastomosis.—Five years ago the first cases had just been recorded by Ballance, Faure and Kennedy, of what has since proven to be the most satisfactory application of the astonishing fact that controllable impulses from given centers may come to traverse a newly established pathway to a paralyzed group of muscles. No better chance for a clear-cut physiological test could have been given than the anastomosis of the peripheral segment of a paralyzed facial nerve with the central end of another motor nerve destined by nature to innervate an entirely distinct musculature. The spinal accessory had been used in the earlier operations, and in our series of fifteen subsequent cases this form of coupling has been adhered to.[30]

From what we now know of the processes of nerve reunion we are the better able to understand the more complete and more prompt restoration of an early graft, not only because of the atrophy of end-organs and muscle bundles, but because of the subsidence of the changes in the peripheral segment which presumably influence the downward projection of the new forming axis-cylinders. The most satisfactory functional results naturally follow an anastomosis made immediately after facial transection, such as may be intentionally performed in cases of troublesome motor spasm. In one of these cases,[31] observed with Dr. H. M. Thomas, restoration of function began within six months and the patient has regained almost complete *emotional* control—acknowledged to be a rare outcome under the best of circumstances.

In like fashion other palsies of important muscles-fields—trigeminal, laryngeal, vesical—lend themselves to nerve grafting with a prospect of improvement in direct relation to the promptness with which the measure is undertaken. Needless to say, the same thing has long been known to be true in the case of the mixed nerves of the extremities, though here another element, that of pain and sensitiveness, comes into play—an element which may stand in the way of the vigorous post-operative measures by electricity and massage necessary to keep the muscles from too great wasting during the long wait for functional restoration. These pains are associated with the return of function in the "protopathic" system of Head, and particularly in children the extremity in which these sensory changes—inevitable after severance of a mixed nerve—are going on, is so sensitive as to preclude massage and electricity.

But this is not the only obstacle to functional restoration by means of anastomoses in the muscle-group paralyses due to poliomyelitis. If, as we surmise, the well-recognized changes, which occur in the sheath of the peripheral segment, represent the chemotactic influences which allure the reforming axone to its old pathway and terminal, it can be readily understood why the outgrowing fibers do not distribute themselves indiscriminately among peripheral fibers, some of which have been long degenerated and some newly degenerated as the result of the anastomosis—why, in other words,

[28] The afferent system from a new aspect. Brain, 1905, Part CX, p. 1.

[29] Bardenheuer's studies of forty-three cases in his personal surgical experience should not be overlooked in a review of this subject. (Mittheilungen aus dem Gebiete der Nervenchirurgie, u. s. w. Deutsche Ztschr. f. Chir., 1908, XCVI, pp. 14-224.)

[30] Purely on the speculative basis that the cortical centers for the tongue were nearer the facial centers than were those for shoulder movements, and that associated movements might consequently be lessened, the hypoglosso-facial form of anastomosis was introduced as an alternative and seems to have been generally followed of late. Associated movements, however, are the same in both instances, and the thickness of speech in one case would appear to be more disturbing than the shoulder droop in the other. I have seen a considerable number of patients after hypoglosso-facial anastomosis, none of them with results comparable to those after accessorio-facial grafting.

[31] On the surgical treatment of facial paralysis. Tr. Am. Surg. Ass., 1907.

the new forming axones should discriminate in favor of the recently severed peripheral fibers which take them back to their original destination. It would presumably be necessary, in order to assure another distribution, to make the graft immediately after the onset of the original paralysis—obviously an absurdly impractical proposal.

We are still making a practice of anastomosing the ends of nerves severed in amputations, and certain unpublished experimental work lends support to the view that terminal neuromata are less likely to form under these circumstances, though, as before stated, this is trusting to the effect of negative polarity. The same measure has been applied to the nerve trunks whose terminals in old amputations have given rise to painful neuromata, with results which are in a measure promising.

Posterior Root Divisions.—Intracranial as well as intraspinal root division, chiefly for painful afflictions in circumscribed skin-fields, doubtless represents a crude method of dealing with these maladies and is justified only on the ground that less simple measures are as yet unavailing. However, even these radical procedures sometimes fail in inexplicable ways, as has been largely true of root divisions for post-zoster pains and for those associated with terminal neuromata. It is difficult to conceive of a central pain set up by a so-called ascending neuritis which will perpetuate discomforts referred to an area rendered permanently anæsthetic by root division. The procedure has been advocated as a form of relief for the gastric crises of tabes, and a few favorable reports of such operations have appeared. Our own restricted experience has not been brilliantly encouraging.

There is a present vogue for posterior root division as a palliative measure for the extreme spasticity of certain cerebral diplegias of the Little type, and though the valuable contributions of Förster and Gottstein and of Clark and Taylor in this direction are based on sound physiological principles [32] just how far we may hope to progress in this direction remains to be seen. "Preliminary reports," particularly in surgery, are too often bred of momentary enthusiasm, and any maladies which overlap, as do these, the boundaries of another specialty demand, for the end results, a long and patient wait with coöperative treatment.

The Facial Neuralgias.—In the trigeminal group of root divisions alone have the surgical results been eminently satisfactory—indeed, they are possibly the most satisfactory of all the major performances of neurological surgery. Unhappily the operation early acquired an unfortunate reputation which special work and perfected methods have not sufficed to entirely set aside; and most patients with major neuralgias present themselves with the full expectation of the loss of an eye, of an unsightly facial paralysis and of a probable recurrence of pain. Haphazard operating bred of inexperience is entirely responsible for this impression, and some of the most shocking examples of bad surgery filter through to the neurological specialist as the end results of former incomplete ganglion operations.

Fortunately, owing to the present widespread employment of the deep alcohol injections, largely due to Patrick's insistence on their effectiveness, much suffering has been spared and many needless and temporizing extracranial operations have been avoided. Neurologists in general would do well to make more use than they do of this form of minor surgery—a straw which shows the direction of the wind. However, in the true major neuralgias the injections soon lose their efficacy and further procrastination is unwise.

In consideration of the average age of the patients, their prolonged suffering, the protracted use of drugs and poor nutritional state, the mortality of the operation for trigeminal root avulsion is surprisingly low. We have had ninety consecutive cases without a fatality; the average hospital residence has been little more than two weeks; it is often impossible for the uninformed to subsequently tell, without sensory tests, upon which side the neurectomy has been performed; and in most instances the outcome is more of a rejuvenation than one sees after almost any other surgical measure. It remains, however—let this point be emphasized again—an operation not to be undertaken by the untrained surgeon. There are comparatively few operators who can resist the temptation to coquette occasionally with the more rare and more difficult operations. It is a failing common to the clan, and a vague feeling of satisfaction is experienced in placing them to one's supposed credit: but it is more often to one's discredit as time proves.

Straightforward and uncomplicated as the neurectomy may prove when done by an experienced team—for it is not an individual event—there are certain clinical facts in regard to these facial neuralgias which our comparatively long series of cases has brought to light. It has become clear that neuralgic pain referred to the trigeminal territory need not be conveyed by the fifth nerve, for in spite of a total and permanent post-operative anæsthesia of this sensory field, three of the patients in the series have had their pain absolutely unmodified by the neurectomy. They are all individuals whose extreme discomforts, referred primarily to the trigeminal area, have been of a continuous rather than a paroxysmal nature. All of them are patients for whom the operation was conducted with some therapeutic misgivings in view of the ineffective results of earlier peripheral injections and neurectomies. These were instances of obvious major neuralgia, rest assured, not cases which could be ascribed to any of the common lesions to which secondary nerve involvement may be ascribed.

[32] Charles Bell found that in the ass, after supramaxillary divisions of both trigemini, the upper lip was no longer elevated in feeding: he, consequently, thought that the nerves might be motor. Experiments in Exner's laboratory suggested that "paralysis" of the laryngeal muscles of the horse may follow section of the corresponding sensory nerve of the larynx. Finally, Sherrington has shown a most striking example as furnished by the ape, for after section of one of the afferent roots from the limb the grasp of the corresponding hand or foot is permanently lost, whereas if a single root is left there may be weakness, but total loss does not follow. In either case, however, the normal grasp may be elicited by stimulation of the appropriate area of the cerebral cortex.

There consequently are other possible sources of origin for the facial neuralgias of this type which we must carefully look for in the future—three sources in particular. Sluder's investigations have shown that an inflammatory involvement of Meckel's ganglion may occasion a more or less continuous and characteristic pain referred to the lower facial areas. Ramsay Hunt's clinical studies on auricular herpes have brought the sensory division of the facial nerve into prominence and have made it clear that geniculate neuralgias are a possible source of confusion; and such a report as Weisenburg has recently made of a case of supposed neuralgia quinti major which had been subjected to numerous peripheral operations and finally to a trigeminal extirpation without relief—a small cerebello-pontine tumor having been the cause of the discomforts from the beginning—makes this a third possible source of diagnostic error which must hereafter be carefully excluded.

Now, after skimming this variety of subjects which have happened to be momentarily of live interest to me, I am conscious that a selection of topics possibly of more general interest might have been crowded into the pages of this address, in which I should have liked, too, to pay generous tribute to those whom I recognize as my own chief examples in general methods of work—Kocher, Sherrington and Halsted—and, fully conscious of the personal note which has been struck, to the many like Horsley, Krause and Chipault who have played and will long continue to play, I trust, a far more important rôle than I can aspire to in this special field.

There is no question but that a training for neurological surgery must come through laboratory experiences, and just as we are indebted to experimentation on the lower animals for almost every fact of importance which has made for the advance of this particular department, so also must we call upon them for the mere practice of hand essential to success in their clinical applications. Those who oppose the employment of animals for such purposes would leave us the only alternative of subjecting our fellow-man, as a lesser creature, to our first crude manipulations.

In work upon the central nervous system many of the principles are widely different from those applicable to other organs of the body and cannot justifiably be put into practice except under the most favorable hospital environment. Even then the primary interest of a single individual can do little without the concentration of effort of an unshifting group of laboratory-trained associates who possess "an infinite capacity for taking pains" in both clinic and operating room. Without the coöperative devotion to this work of G. J. Heuer, S. J. Crowe and Emil Goetsch any personal efforts toward meeting the many problems which daily confront us would have been entirely unavailing, and the operative procedures themselves have often been saved from disaster by Dr. Davis' skillful handling of the anæsthetic.

Neurological surgery is fascinating, and will long continue an important and profitable field for intensive cultivation, partly because it has been largely unworked from an operative standpoint, partly because it deals with one of the two most important systems of the body—nervous and circulatory. It is gratifying to see that a number of young men are fitting themselves to specialize in it, with a preparation which makes envious one who has wriggled into the subject and, like the proverbial squid, has left little but a trail of ink behind him.

THE CAMMIDGE TEST IN EXPERIMENTAL PANCREATITIS AND OTHER CONDITIONS.

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(From the Hunterian Laboratory of Experimental Pathology.)

A comprehensive discussion and analysis of the observations and experiments of the numerous writers who have made contributions to this subject would be of interest but does not seem to come within the scope of this paper. We may refer to recent publications of Hess, Hagen, Elösser, Kinnicutt and Edsall where may be found excellent reviews and discussions of the whole question and its extensive literature. It is interesting to note how varied are the tones of different writers ranging all the way from the extreme optimism of Cammidge, Mayo-Robson, Watson and Barker to absolute pessimism of Haldane, Hess, Röth, Grimbert and Bernier. We are particularly interested in the reports of different investigators who have studied the urine of animals in which pancreatic injury had been produced and we may review briefly some of these reports which vary in such an amazing degree.

Elösser performed experiments to support the theory of Cammidge that the reaction in the urine is due to the splitting of body fat into fatty acids and glycerine (fat necroses). He injected glycerine diluted with salt solution into the peritoneal cavities of two dogs. Both animals, after the injection, gave a positive Cammidge test, but he makes no note that the urine of these dogs was examined before the injection, and it is possible in the light of other experiments, that controls would have been positive. Cammidge tests "A" and "B" were used.

Schmidt reports a valuable series of animal experiments and among other things states that intraperitoneal glycerine injections do *not* cause a positive Cammidge test. He produced experimental pancreatitis by ligating or crushing the gland or by injecting oil into the parenchyma. The urine of

these animals before operation was negative, but usually positive for a few days after the injury. He gives no record of the pathology (gross or microscopical) of the cases tested, and does not test the urine for a space of more than one week. Surely if the test is specific for chronic pancreatitis, we should expect a positive test during many weeks or months following the acute pancreatitis. Our experiments indicate that an acute pancreatitis is always followed by a definite chronic interstitial pancreatitis which is constant and permanent, at least for months. Schmidt found a positive Cammidge test following resolution of pneumonia, peritonitis, and experimental injury to the liver. He believes that the reaction of the urine is due to a pentose formed by *nuclear destruction* in the pancreas or any other body tissue. It may be noted at this point that Watson found a strikingly positive Cammidge reaction in cases of pneumonia and malaria; but he is very enthusiastic about the test and considers it to be of great diagnostic value in pancreatitis. These observations agree with some of ours given below where it is evident that there is extensive cell destruction in the body (see chloroform liver necrosis) and in such conditions a positive Cammidge test is the rule.

Eichler and Shirokauer report an excellent series of experiments on dogs. They produced pancreatitis by ligating or crushing the gland. The urinary findings were very carefully studied, and the pathological findings noted at the end of each experiment—a matter of one or two weeks. Every animal gave a negative Cammidge test before operation and many gave the same negative test after the pancreas had been injured. In some experiments the urine gave a positive test for a few days following the pancreatic insult, then a negative test for 3-4 days and again a positive period of several days. The writers are skeptical about the value of the test.

It is interesting to note that different observations on the melting point of the Cammidge crystals vary as widely as do the reports on the urinary findings in men and animals. Cammidge claims that the crystals isolated by his method from the urine of men or dogs suffering with pancreatitis melt sharply at 178-180° C. and concludes that it is a pentosazone. Grimbert and Bernier give the melting point of the crystals as 137-138° C. and state that they can be obtained from normal urine. Caro and Wörner give the melting point as 150-160° C. They study the parabromphenylhydrazine as well and conclude from their analyses that the substance is a glycuronic acid. Goodman gives the melting point as about 155° C. and is in accord with Caro and Wörner. Ellenbeck gives the melting point as variable (163-184°), in different cases and believes that this indicates a relation to the pentoses and glycuronic acid.

A review of these reports would indicate that the different workers were examining different substances or perhaps a compound of many substances in which the constituents varied under different conditions. Grimbert and Bernier are of the opinion that the test is valueless because of its presence in normal urine. They believe that the form and type of the crystals are dependent upon the concentration of the solutions and the salt content. Our experience confirms this in part, and we believe that the ease with which the acid dissolves the crystals depends in great measure upon the delicacy of the crystals. If we can modify the morphology of the crystals by changing the concentration of the solution, the salt content and the rapidity of cooling we thus modify the solubility of the crystals. But the solubility in 33 per cent sulphuric acid is considered of diagnostic value (Cammidge). Schumm and Hegler state that the solubility of the crystals in acid is not in any way specific, and they believe that the majority of the positive tests are due to a small amount of grape sugar which is present in the urine but in insufficient amount to give a Fehling's test.

These facts do not tend to strengthen one's faith in this test as the essential substance does not seem to be a definite chemical entity or if so has not been isolated in a satisfactory manner.

It is interesting to review some recent experiments of Speese and Goodman which differ in some degree with the findings in our series of experiments. In their first communication they state that normal men, dogs, and rabbits never give a positive Cammidge test, but in a second paper they state that one normal dog in the 17 examined gave a positive test. They say that this dog was discarded as of no value for their experiments, but we feel that it would have been of interest to follow that normal animal to determine how long the reaction persisted in his urine. We are convinced from our own experiments that repeated observations on animals before the production of experimental pancreatitis will show that a higher per cent of normal animals give a positive Cammidge test. A critical review of the experiments of Speese and Goodman does not convince one that they are justified in their conclusion—"The Cammidge reaction is a constant feature of hemorrhagic pancreatitis, in mechanical injuries of the gland (crushing of the tail, partial extirpation) and in total extirpation."

In a recent communication Cammidge has reported some observations on animals which are in harmony with his observations on human cases. It is very easy to criticise this series of experiments, and requires but little space as he reports observations on a few animals in a rather incomplete manner. The pancreatitis was produced in a foreign laboratory by injection of turpentine into the gland or by passing a ligature into the pancreatic duct. No careful protocols of the experiments are given. The urine was sent a considerable distance in bottles preserved with toluol. Cammidge found the tests to be uniformly positive and to resemble in every way those made in human cases. The crystals were similar and the melting point identical (178-80° C.).

METHOD.

The method used in this series of experiments is that described by Cammidge as "Test C." The tests have been made by four different workers, B. S. Chaffee, R. F. Fisher, Dr. J. H. King and Dr. G. H. Whipple. Often duplicate tests were made by two or more of these workers, and every effort was made to eliminate the personal equation. The crystals were examined by the different workers and the opinions compared, the solubility

tested with 33 per cent sulphuric acid, and the types of crystals described in the histories. The tests were done carefully, and it was found that they were rather time-consuming. No difference was noted between clean, filtered cage urine and catheterized urine, but the latter was used when available. The filtered urine was freed from albumen and sugar, if necessary, and 20 cc. were taken for each test. To this is added 1 cc. of concentrated hydrochloric acid and the mixture boiled gently for 10 minutes on a sand bath in a small Erlenmeyer flask with a funnel as a condenser. The flask is then cooled and the solution made up to a volume of 20 cc. Lead carbonate (4 grams) is then added and allowed to stand for some time until all the acid is neutralized. Filter until clear. To this clear filtrate basic lead acetate (4 grams) is added to remove the glycuronic acid by precipitation. Filter until clear and add sodium sulphate (2 grams). Heat to boiling, cool and filter which removes most of the lead. 10 cc. of this clear filtrate is diluted to 17 cc. with distilled water and to it is added sodium acetate (2 grams), phenylhydrazine hydrochlorate (0.8 gram) and 1 cc. of 50 per cent acetic acid. This mixture is placed in a small Erlenmeyer flask with a funnel as a condenser, and boiled gently for 10 minutes on a sand bath. Filter hot through a hot, moist filter, and if necessary, make up the filtrate to a volume of 15 cc. by adding a little distilled water. The Cammidge crystals come down on standing, are examined under the microscope and their solubility tested with 33 per cent sulphuric acid. The typical crystals should dissolve in a few seconds after the acid touches them, and this is held to be an important diagnostic point by Cammidge.

ACUTE AND CHRONIC PANCREATITIS.

Dog 72. Medium-Sized Female Fox Terrier. Weight 20 lbs.
Nov. 13. *Injection of Bile (2 cc.) Into the Pancreatic Duct.*

Date.	Urine.	Reaction.	Alb.	Reducing bodies.	Cammidge test.	Remarks.
Nov. 15	Cage.	Acid.	++	—	+	
Nov. 16	Cage.	Acid.	+	—	+	
Nov. 16	Cage.	Alk.	Tr.	—	+	
Nov. 17	Cage.	Alk.	+	—	+	
Nov. 18	Cath.	Acid.	+	—	+	
Nov. 18	Cath.	Alk.	+	—	+	
Nov. 19	Cage.	Alk.	+	—	+	
Nov. 20	Cath.	Acid.	Tr.	—	+	Very few crystals.
Nov. 22	Cage.	Acid.	Tr.	—	+	Do.
Nov. 23	Cage.	Alk.	Tr.	—	—	
Nov. 24	Cage.	Acid.	—	—	+	Few crystals.
Nov. 25	Cage.	Acid.	—	—	—	
Nov. 28	Cath.	Acid.	—	—	+	Very few crystals.
Dec. 4	Cage.	Acid.	—	—	—	
Dec. 8	Operation and removal of piece of pancreas. Chronic pancreatitis.					
Dec. 13	Cage.	Neutral.	—	—	+	Little blood in urine.
Dec. 20	Cage.	Neutral.	—	—	±	Atypical crystals very resistant to acid.
Dec. 23	Cage.	Acid.	—	—	++	Perfectly typical hair-like crystals.
May 1	Cath.	Acid.	—	Faint?	—	Very few large insoluble crystals.
May 1	Cath.	Acid.		—	—	
May 17	Autopsy. Chronic pancreatitis.					
Dec. 23	Purified crystals; melting point 153-4° C.					

Nov. 13, 1909. The dog is strong and well. At 12 M. an *operation* through right rectus. The large pancreatic duct isolated and 2 cc. of pig's bile injected pretty rapidly into the duct. In a few moments a diffuse ecchymotic appearance was made out involving practically all of the pancreatic tissue, showing that the injection had been pretty uniform. After 20 minutes there were many ecchymoses throughout the greater part of the pancreas and a faintly bile-tinged oedema with swelling and increased resistance in the pancreatic tissue. There was a little bleeding around the site of injection. The abdomen was closed in layers and the animal made a good recovery from the anæsthetic.

Nov. 14. Dog appears pretty sick and no clean urine was obtained.

Nov. 15. Dog is about the same.

Nov. 16. The animal drinks a large amount of water and has passed copious, pale urine of alkaline reaction.

Nov. 17. The animal is improving definitely.

Nov. 18-20. Dog is doing very well. The abdominal wound is almost completely healed.

Nov. 22. Dog seems quite well.

Nov. 23-29. Dog is quite active and seems very well and strong.

Dec. 8. *Exploratory laparotomy.* The peritoneal cavity shows many delicate adhesions around the pancreas involving the omentum and the duodenum. These are broken through with little difficulty, and the pancreas is completely exposed and brought out in the wound for examination. It has a very abnormal appearance. It is pale, quite nodular and irregular, full of depressed scars and very firm to the touch. The gland is about one-half to two-thirds of its normal size and all parts of the parenchyma are involved in this change. There are no fat necroses to be seen nor any hemorrhage. The depressed scars have a translucent bluish appearance and are evidently due to an increase in connective tissue. A good sized piece of pancreatic tissue was removed for microscopical examination, and the abdomen closed.

Microscopical section. The lobules are pretty sharply marked out, and there is a definite increase in cellular connective tissue between the lobules, associated with the larger ducts and vessels. Some of the lobules are almost normal as regards their acinar units, but many show a very diffuse increase in fibrous connective tissue. Here the acini may be greatly distorted, either shrunken and embedded in connective tissue or dilated with pink, hyaline-like casts. In other areas are found large clumps of mononuclear cells embedded in patches of connective tissue replacing parts of lobules. In some areas are seen accumulations of large phagocytes packed full of yellow, granular, blood pigment evidently the result of a healed, hemorrhagic focus. Some of the smaller pancreatic ducts are embedded in thick, new-formed connective tissue and full of pink, uniformly staining colloid material appearing as though they were much obstructed. The gland shows definite evidence of a partially healed inflammation and may be classed as a *subacute* or *chronic pancreatitis.*

Dec. 9. The animal seems well. The wound is rather œdematous.

Dec. 11. The animal is active and well, but the wound rather swollen and may break down.

Dec. 17. Dog is quite well, weighs 20 lbs.

Dec. 23. Dog is quite normal in every respect, and is put outside in the yard.

April 4. Animal returned to cage for observation, weighs 20 lbs., is strong and comparatively healthy except for mange.

May 1. Dog again placed in cage for observation and study of urine. The animal is in good health and normal except for a bad infection with mange and rather prominent pendulous teats.

May 10. Dog dipped in a solution to cure the mange.

May 17. Dog is very sick, found lying on its side. The vagina, teats, and all the breast tissue are greatly swollen and œdematous. The tissue is red and suggests a diffuse phlegmon of the abdominal tissues. Death in the afternoon.

Autopsy shortly after death. The breast tissue shows a great deal of œdema and injection but no apparent increase in glandular tissue.

Microscopical section shows a true mixed tumor of the breast tissue with much new growth of ducts and acini together with nests of cartilage. In addition there is an acute inflammation causing a great deal of œdema of all the tissues. Leucocytes are present in the interstitial tissue and the ducts, lymphatics and blood vessels. Thorax is normal. Spleen, kidneys, liver, and gastro-intestinal tract show nothing of interest in gross or microscopically. The uterus shows a nodular, cystic condition together with hemorrhage in the mucosa.

Pancreas is deep red and translucent. The parenchyma shows a pretty uniform change, and the organ is definitely smaller than normal, but does not look as abnormal as at the time of operation. The lobulation is conspicuous, and the surface has a warty appearance. The lower arm is more involved than the upper, but no part of the pancreas has escaped. The head shows several conspicuous bluish scars where all the parenchyma has been replaced by new tissue. Much of the parenchyma is speckled with tiny opacities; some of them measuring 1 mm. in diameter.

Microscopical sections show much less change than is noted above in the tissue removed at operation. The connective tissue scars are perfectly definite but much smaller and made up of dense connective tissue with a few mononuclear cells. The acini are considerably distorted in size; many of them being small and rather compressed looking, but a good many are large and quite normal in appearance. The ducts and islands show no striking abnormality. There seems to have been some recovery during the months following the removal of the control bit of tissue, but there is a definite *chronic pancreatitis.*

Dog 81. Large, Black and White Mongrel, Female, Weight 44½ lbs.

Injection of Bile Into Pancreatic Duct.

Date.	Urine.	Reaction.	Alb.	Reducing bodies.	Cammidge test.	Remarks.
Dec. 22	Cage.	Alk.	—	—	+	Many typical hair-like crystals.
Dec. 23	Cage.	Alk.	—	—	+	Many typical hair-like crystals.
Jan. 6	Operation. Bile (4½ cc.) injected into pancreatic duct. Acute pancreatitis.					
Jan. 6	Cage.	Alk.	Tr.	—	+	Crystals have typical shape but dissolve slowly in acid.
Feb. 1	Operation. Bile (7 cc.) injected into pancreatic duct. Acute and chronic pancreatitis.					
Feb. 2	Cath.	Alk.	Tr.	—	—	(Urine) 200 cc. treated as described by Cammidge to obtain large amounts of crystals for melting point.
Feb. 3	Cage.	Alk.	Tr.	—	—	
Feb. 5	Cage.	Alk.	Tr.	—	—	
Feb. 10	Cage.	Alk.	+	—	±	Fine yellow crystals of typical sheaf form but slowly soluble,
Feb. 28	Cage.	—	—	—	—	
May 1	Cath.	Acid.	—	—	±	Burs of very fine needles which dissolve slowly.
May 2	Cath.	Acid.	—	—	+	Large amount of fine needles and some coarse crystals.
June 30	Autopsy. Extreme chronic pancreatitis.					

Dec. 18. Operation at the root of the neck to establish a thoracic duct fistula. The operation was unsatisfactory and the animal was allowed to recover.

Dec. 19-21. The neck wound is granulating and the animal is quite active.

Dec. 22-25. Dog is noisy and active as usual.

Jan. 6. The neck wound has completely healed. The animal is quite strong and very active. *Operation* through the right rectus with exposure of the larger pancreatic duct. 4½ cc. of pig's bile were injected slowly into the pancreatic duct. Hemorrhagic specks and bile-stained œdema appeared in a few moments indicating a rather uneven distribution of the bile in the pancreas. The head and middle portions of the lower arm of the pancreas show extensive hemorrhages and marked œdema, but the upper arm shows relatively little involvement. The abdomen is closed in the usual way.

Jan. 7. Animal does not seem very sick. There is no vomiting and appetite is good.

Jan. 8. Dog is very active and hungry. The wound is clean and healing well.

Jan. 9. Animal has scratched a part of the wound, tearing it open down to the muscular layer.

Jan. 11. Dog is quite well, and the abdominal wound is granulating in a healthy manner.

Jan. 14-18. Dog is quite well.

Feb. 1. Ether anæsthesia, 10.30 a. m. *Operation.* The abdominal cavity shows many dense adhesions around the head of the pancreas and duodenum. The pancreatic duct is exposed as before, but much bleeding is encountered. The head and lower arm of the pancreas presents a very pale, nodular appearance, and is hard and resistant to the touch. There is evidently a well-marked *chronic pancreatitis.* 7 cc. of pig's bile injected rapidly into the pancreatic duct. In a few moments ecchymoses and œdema appear all through the head and lower arm of the pancreas. The upper arm is not visible and no attempt was made to release the dense adhesions between it and the lower curvature of the stomach. The abdomen is closed as usual.

Feb. 2. The animal is not especially shocked. There is no vomiting. A large amount of water is consumed and a corresponding amount of clear urine obtained by catheter.

Feb. 3. The animal is much the same.

Feb. 4. The animal is doing well and recovering rapidly.

Feb. 6. Dog appears quite normal.

Feb. 14. Dog is very noisy and active. The abdomen has completely healed, and the animal is put in the yard.

Feb. 28. Animal returned to cage for observation and seems normal in every way. Cammidge test negative.

April 27-30. Animal again in cage under observation, and appears normal. Urine obtained by catheter for Cammidge test.

May 1-June 15. Animal is under observation in cage and seems quite normal. Feces are abundant and appetite vigorous.

June 30. Dog weighs 42 lbs., and is perfectly well. Killed with ether and bleeding. *Autopsy* at once. There are many old adhesions all about the duodenum binding it to the liver and adjacent structures. Dense adhesions are present over all parts of the pancreas, and it is dissected free with some difficulty. The fat in the omentum is well preserved and quite normal. *Pancreas.* The gland is reduced to a nodular cord of tissue not over ¾ cm. wide in any part and about ⅓ cm. thick. The tissue as a rule is tough, elastic and has a bluish translucence as though connective tissue were a dominant element. There are small nodules of pale, opaque, grayish tissue which resemble gland parenchyma, but are very firm and elastic. These nodules are inconspicuous, and the larger ones which are situated in the head of the pancreas do not exceed ⅔ cm. in diameter. The blood vessels and ducts are thick and conspicuous.

Microscopical sections. The greater part of the gland is replaced by very dense scar tissue in which the distorted and thickened pancreatic ducts are embedded. Here and there are small nests of cells which may be distorted acini or islands of Langerhans. There are a few spherical nodules which are widely separated and surrounded by a capsule of scar tissue, in which the acini and islands are fairly well preserved and recognizable. Even in the best preserved nodules there is an abundance of connective tissue which distorts the acini and obscures the gland units. The healing has been complete and there are no pigment bearing cells which may mark out the areas of hemorrhage in the gland. This is a picture of *extreme chronic pancreatitis.* The stomach and intestines are greatly distended with partly digested food and the rectum is distended with pale, fatty, fecal material.

To review briefly these two experiments (dogs 72 and 81) it is clear that both animals were suffering primarily from acute hemorrhagic pancreatitis induced by the injection of bile into the pancreatic duct and secondarily from a chronic fibrous pancreatitis resulting from the healing of the acute inflammatory process. The pathological changes have been controlled by inspection at operation, microscopical examination and autopsy. Both animals were under observation for a considerable time with varying results. Dog 72 gave a constant Cammidge test during the acute stage, but the test was uncertain or absent as the lesion became more chronic. Dog 81 gave a *positive* test when in perfect health before the operation, but gave a *negative* Cammidge on several occasions after the pancreas had been injured. *Autopsy* of dog 81 revealed an extreme grade of chronic fibrous pancreatitis.

DOG 84. ACTIVE FOX TERRIER, FEMALE, WEIGHT 16¼ LBS.

Date.	Urine.	Reaction.	Alb.	Reducing bodies.	Cammidge test.	Remarks.
Dec. 29	Cath.	Acid.	—	—	—	Few coarse crystals.
Jan. 11	Cage.	Acid.	—	—	—	Many fine crystals resistant to acid.
Jan. 12	Cage.	Acid.	—	—	—	
Jan. 13	Cage.	Acid.	—	—	—	Meat diet—300 grams daily.
Jan. 14	Cage.	Acid.	—	—	—	
Jan. 15	Cage.	Acid.	—	—	—	
Jan. 18	Cage.	Acid.	—	—	—	
Mar. 10	Operation. Bile (5 cc.) injected into pancreatic duct.					
Apl. 19	Operation and removal of piece of pancreas. Extreme chronic pancreatitis.					
May 1	Cath.	Acid.	—	F'nt +	—	Fine, grass-blade type of crystal in very small amount, soluble in one minute.
May 1	Cath.	Acid.	—	F'nt +	—	

Jan. 11-18. Animal on uniform meat diet—300 grams of lean meat daily.

Jan. 25. Weight 19 lbs. Animal is in excellent condition.

March 4. Weight 19½ lbs. Animal is quite well.

March 10. *Operation* through right rectus. The pancreatic duct was exposed and 5 cc. of pig's bile injected rapidly into it. Numerous ecchymoses appeared at once in all parts of the pancreatic parenchyma, but more numerous in the lower arm and head of the gland. Bile-stained œdema was conspicuous 5 minutes later. In the afternoon the animal was greatly shocked; repeated vomiting.

March 11. Animal is very sick, vomiting repeatedly and will not eat.

March 12. Dog is very sick and rather dull, vomiting repeatedly. Abdominal wound is dry and healing well. Water introduced into the stomach by a stomach tube was vomited at once. Very little urine obtained by catheter for the study of ferments.

March 13. Dog shows slight signs of improvement. Diarrhœa is a conspicuous feature, the feces yellow and fatty in appearance with a little admixture of blood. Abdomen is very tender to palpation, but wound is healing well.

March 14. Animal improved and taking food. Diarrhœa still present and of the same type as described above. Urine very scanty and high colored.

March 16. Improvement slow and animal walks about the cage well. Diarrhœa persists.

March 17. Dog looks pretty well, weighs 15 lbs. Wound practically healed. Urine abundant, clear and pale.

March 24. Animal is quite well and active and has a very vigorous appetite, but is losing weight—weighs 13½ lbs. Feces are very abundant, cream yellow and pasty.

April 4. Weighs 14½ lbs. Stools are very abundant, pale and fatty looking. Appetite is ravenous and animal will eat anything placed before her in almost any amount.

April 19. *Operation.* The abdominal cavity contains many old adhesions about the head of the duodenum binding all the structures together. There is considerable bleeding due to separation and tearing of these adhesions. The pancreas is exposed with difficulty and presents a very remarkable appearance. It is greatly distorted and practically no normal tissue is to be made out. There is only one small piece of pancreatic tissue in the head which has approximately a normal appearance. This nodule measures about 1½ cm. in long diameter. Here the pancreatic lobulation can be made out, and the parenchyma is very opaque and grayish. The remaining part of the pancreas is represented by a flat fibrous band. The tissue is very flabby and can scarcely be palpated. It resembles the tissue found after ligation of the pancreatic duct where the pancreatic tissue has undergone extreme atrophy. A small piece is removed from the lower arm close to the nodule of parenchyma described. The tissue is very tough and elastic, and in gross the parenchyma is very inconspicuous or almost absent.

Microscopical sections. The tissue is very difficult to cut owing to the fact that it is made up in great part of dense, fibrous tissue. The sections show an extreme grade of *chronic pancreatitis.* There is no normal parenchyma to be seen. A few small islands of pancreatic tissue are left embedded in dense connective tissue. The islands are inconspicuous and greatly distorted, but the acini have suffered much more and scarcely a normal acinus is visible. They are all distorted and embedded in connective tissue full of mononuclear cells. In places there are huge nests of phagocytes containing yellow granular pigment, the results of hemorrhage during the acute stage. Even the collecting ducts of the pancreas are greatly distorted, narrowed and embedded in dense scar tissue.

April 20. Animal is well and wound healing perfectly.

May 1. Animal is quite well. Feces are abundant and fatty, and the appetite is ravenous.

June 9. Condition remains the same. Weighs 17 lbs.

This animal (dog 84) is of considerable interest for several reasons. Repeated observations under fixed conditions and uniform diet gave no Cammidge test before operation. Injection of bile into the pancreatic duct caused a severe pancreatitis which almost resulted fatally and which in healing produced an *extreme chronic pancreatitis.* The dog clinically showed all the signs of advanced chronic pancreatitis, abundant fatty stools, huge appetite and low carbohydrate tolerance. Removal of a piece of pancreatic tissue demonstrated an extreme grade of chronic fibrous pancreatitis in microscopical sections. Yet observations during this period gave a *negative* Cammidge test (see chart 84).

Nov. 3. *Operation* through right rectus and isolation of pancreatic duct. 1½ cc. of pig's bile was injected into the pancreas with a pretty uniform distribution as indicated by the ecchymoses.

Nov. 4. Dog is not very sick, no vomiting.

Nov. 5. Animal appears practically well.

Nov. 24. Dog is quite well and active. *Operation* and removal of some pancreatic tissue at the end of the lower arm. The upper limb and head of the gland appeared a little more nodular, paler and firmer than normal, but the piece removed was very firm and nodular in appearance.

Dog 67. Small Fox Terrier, Male, Weight 14 lbs.
Nov. 3. *Injection of Bile (1½ cc.) Into Pancreatic Duct.*

Date.	Urine.	Reaction.	Alb.	Reducing bodies.	Cammidge test.	Remarks.
Nov. 3	Cage.	(?)	(?)	—	—	Before operation.
Nov. 4	Cage.	Acid.	—	+	+	
Nov. 10	Cage.	Acid.	—	—	+	
Nov. 11	Cage.	Acid.	—	—	+	
Nov. 12	Cage.	Acid.	—	—	+	
Nov. 15	Cage.	Acid.	—	—	—	
Nov. 24	Cage.	Acid.	—	—	—	
Nov. 24	Operation. Removal of piece of pancreas. Subacute pancreatitis.					
Apl. 16	Operation. Removal of second piece of pancreas. Normal (?)					
May 1	Cage.	Acid.	—	—	±	Very small amount of crystals, irregular burs of long hair-like form soluble in 30 seconds.
June 27	Autopsy. Slight chronic pancreatitis.					

Microscopical section. There is an advanced grade of chronic diffuse pancreatitis together with some acute inflammation. The pancreatic acini are distorted and separated from each other by a very cellular connective tissue full of mononuclear cells of all types. There are also phagocytes full of yellow, granular pigment. The interlobar tissue is very œdematous and full of blood-vessels and young fibroblasts with some recent areas of hemorrhage in some places. The pancreatic duct is relatively less affected but embedded in masses of scar tissue in some areas.

Dec. 4. Animal has recovered from the operation perfectly.

Dec. 11-March 13. Animal in yard and quite well.

April 16. Weight 20 lbs. Operation as before and removal of the second piece of pancreas. The gland appears more nearly normal than at first operation, except for the presence of many dense adhesions at the site of former operations.

Microscopical section. The gland tissue is almost normal. There are a few small connective tissue scars here and there in some of the lobules, but practically all the acini are normal in every respect.

May 1. Dog is quite well. Urine obtained in large amount for the Cammidge test was practically negative.

June 27. Dog is in perfect health—weight about 20 lbs. Killed with ether. *Autopsy* at once. There are many dense adhesions around the duodenum. Thorax: heart and lungs are all normal. Spleen, stomach, intestines, kidneys and liver are perfectly normal. *Pancreas:* almost all of the lower arm has been removed and only a bit of it close to the duodenum remains embedded in a mass of adhesions. This pancreatic tissue is firm, nodular and pale but the parenchyma of the head and upper arm shows much less change. Much of the gland here is normal, but there are areas here and there where it is evident that there is an increase in scar-tissue. These areas are more nodular and appear as depressions in the gland tissue and are tougher than the normal pancreas.

Microscopical sections show a slight grade of chronic pancreatitis. The connective tissue is conspicuous around some of the smaller ducts and in some of the lobules in these areas there are small scars, but the acini as a rule are normal.

Nov. 15. *Operation* through right rectus and resection of a greater part of the pancreatic gland. About 4 cm. of the distal portion of the lower arm of the pancreas was left in situ. A few small bits of pancreatic tissue close to the duodenum were not removed.

Nov. 16. Animal is doing well. Urine shows a trace of albumen and some sugar.

Nov. 17. Sugar has disappeared from the urine, and its pres-

Dog 73. Small, Female, Fox Terrier, Weight 10¾ lbs.
Nov. 15. *Resection of Part of Pancreas.*

Date.	Urine.	Reaction.	Alb.	Reducing bodies.	Cammidge test.	Remarks.
Nov. 18	Cage.	Acid.	Tr	—	—	
Nov. 21	Cage.	Acid.	—	—	—	
Nov. 23	Cage.	Acid.	—	—	—	
Dec. 13	Cage.	Acid.	—	—	+	Typical crystals.

ence was undoubtedly explained by the long anæsthesia of the preceding day.

Nov. 18-23. Animal is quite well. Urine shows no sugar.

Nov. 24-30. Animal is slowly losing weight. The urine contains no sugar. The feces are very abundant, fatty and the appetite enormous.

Dec. 6. Animal given 10 grams of cane sugar dissolved in 100 cc. of water by mouth.

Dec. 7. Urine contains no sugar. The dog again given sugar, 30 grams, dissolved in water. Urine obtained in the afternoon contained sugar.

Dec. 8. Weight 8¾ lbs. Urine contains no sugar.

Dec. 16. *Operation* through right rectus for exploration. The remnant of the pancreas is closely adherent to the wall of the duodenum and the liver by dense adhesions. It is very pale and nodular, measuring about 2½ x 1 x ⅓ cm. A small piece was removed for microscopical section.

Dec. 17-18. Animal recovering rapidly from operation.

Dec. 20. Dog found dead in cage.

Autopsy. The peritoneum showed no acute inflammation. Thorax, heart and lungs negative. Spleen and liver were normal. The other viscera were negative except the pancreas.

The *pancreas* remnants were removed entire, adherent to the duodenum. Microscopical sections show an advanced grade of chronic diffuse pancreatitis throughout all the parenchyma. The lobules of the gland are separated by dense bands of connective tissue. The acini are quite abnormal, embedded usually in a rich stroma of connective tissue and mononuclear cells; some of them seem relatively normal. The collecting tubules are rather inconspicuous, but some of them contain organized casts of a hyaline nature.

Dog 60. Mongrel, Female, Weight 17 lbs.
Oct. 26. *Injection of Bile (4 cc.) Into Pancreatic Duct.*

Date.	Urine.	Reaction.	Alb.	Reducing bodies.	Cammidge test.	Remarks.
Oct. 27	Autopsy.	Acid.	+	—	+	Abundant typical crystals.

Oct. 26. *Operation* through right rectus and injection of 4 cc. of fresh pig's bile into the pancreatic duct. Immediately hemorrhages appeared throughout the gland and there was an intense œdema. Wound closed in the usual manner. Animal was very sick in the afternoon.

Oct. 27. Animal is moribund. Killed with ether. *Autopsy* at once. The peritoneal cavity contains about 40 cc. of blood-tinged fluid, and the serous surfaces everywhere are greatly injected. The urine used for Cammidge test was obtained from the bladder at autopsy and gave very typical sheaves of crystals. The viscera except for the pancreas show no lesions of interest. The *pancreas* is very large, firm and œdematous, and about twice the normal size. It is speckled over with fat necroses which are present as well in the nearby fat. The pancreatic tissue is mottled with hemorrhagic splotches. Some of the tissue in the head of the gland is green, opaque and necrotic looking.

Microscopical section shows a typical picture of acute hemorrhagic pancreatitis with much fat necrosis and hemorrhage.

Dog 64. Medium Sized Mongrel, Female.
Nov. 2. *Injection of Bile (2 cc.) Into the Pancreatic Duct.*

Date.	Urine.	Reaction.	Alb.	Reducing bodies.	Cammidge test.	Remarks.
Nov. 3	Cage.	Acid.	—	—	+	

Nov. 2. *Operation* as usual and injection of 2 cc. of pig's bile into the pancreatic duct. The injection entered the head and a part of both arms as shown by the ecchymoses and bile-stained œdema which appeared in a few moments.

Nov. 3. Animal sacrificed for class demonstration with autopsy. The peritoneal cavity contains some blood-tinged fluid and shows a beginning peritonitis. The viscera are negative except for the pancreas. The *pancreas* is large, firm, œdematous, and presents a mottled appearance, the gland tissue being of a pinkish color, mottled over with many small ecchymoses. There are numerous large chalky fat necroses. On section hemorrhages are found to be much more numerous in the core of the gland, close to the ducts than in the parenchyma just under the peritoneum. The distal half of the lower arm has escaped much of this acute process and looks relatively normal.

The last three experiments are incomplete and rather unsatisfactory: they were early experiments and not carefully controlled by observations before operation. It is interesting to note that dog 73 gave no Cammidge test shortly after resection of most of the pancreas but gave a positive test a month later, shortly before the death of the animal. *Autopsy* showed chronic pancreatitis in the remaining bit of pancreas. Dog 67 gave a positive test during the acute period of the disease but a negative test latter, when operation revealed a subacute pancreatitis. This experiment seems to give some evidence that the pancreas can recover from a sub-acute condition and return almost to normal.

CHLOROFORM LIVER NECROSIS.

Dog 58. Large Black Mongrel, Male, Weight 27 lbs.
Oct. 22. *Injection of Chloroform Into Portal Vein.*

Date.	Urine.	Reaction.	Alb.	Reducing bodies.	Cammidge test.	Remarks.
Oct. 25	Cage.	Acid.	—	—	+	
Oct. 26	Cage.	Acid.	—	—	+	
Nov. 29	Second operation. 1 cc. chloroform injected into portal vein.					
Nov. 30	Floor.	Acid.	—	—	—	
Dec. 1	Floor.	Acid.	—	—	+	
Dec. 2	Cath.	Acid.	—	—	+	Urine obtained from bladder at autopsy.

Oct. 22. *Operation* through right rectus and injection of 1 cc. of chloroform (undiluted) into portal vein.

Oct. 23. Animal rather sick, but will eat.

Oct. 24-30. Rapid improvement to normal.

Nov. 2-16. Dog is quite active and well in the yard.

Nov. 29. Second *operation* identical with the first.

Dec. 2. Animal has torn the wound open permitting escape of intestines. Killed with ether. *Autopsy* at once. The peritoneal cavity shows considerable injection, and a little fresh peritonitis over the areas of damage in the liver parenchyma. Heart, lungs, thorax, spleen, intestine are all normal. Pancreas shows a little injection in some places, but there are no fat necroses and no hemorrhages. Liver is very large and swollen. There are a few depressed bluish scars evidently the result of the first injection. There are extensive areas of complete necrosis of the liver tissue which appear as greenish gray, opaque areas surrounded by a thin zone of hemorrhage. The liver tissue everywhere is very deep purplish red and friable. The areas of necroses show a haphazard distribution.

Microscopical sections. Pancreas, spleen, and other organs show nothing of importance. The *liver* shows many connective tissue scars which are relatively inconspicuous and in all instances situated about the portal tissue causing a certain amount of distortion of the nearby lobules. There is some proliferation of bile-ducts but this is relatively inconspicuous. In addition there are large and small, hyaline necroses affecting all parts of the liver. Some of the larger areas measure several centimetres in diameter, and present a uniform, hyaline appearance in the center with a margin of inflammatory tissue. There are smaller discrete, hyaline necroses involving one or more lobules or only a part of a single lobule. Here the liver cells present a hyaline appearance and are associated with many mononuclear and polymorphonuclear cells. The blood-vessels are injected in these regions. The areas of necrosis are usually intimately associated with the portal spaces.

Dog 87. Bull Terrier, Female, Weight 18½ lbs.
Jan. 25. *Chloroform Anæsthesia.*

Date.	Urine.	Reaction.	Alb.	Reducing bodies.	Cammidge test.	Remarks.
Jan. 27	Cage.	Acid.	+	—	+	Albumen removed.
Jan. 27	Cage.	Acid.	+	—	+	Albumen not removed.
Jan. 27	Operation and removal of piece of liver. Central necrosis and fatty degeneration.					

Jan. 25. *Chloroform anæsthesia* for *2 hours*, ⅘ of an ounce of chloroform used. Anæsthetic was well taken. At the end of anæsthesia the animal was bled 75 cc. from the jugular and infused with 200 cc. of normal saline plus 2 grams of calcium lactate.

Jan. 26. The animal is recovering rapidly.

Jan. 27, 10.30 a. m. *Operation* and removal of a small, wedge-shaped piece of liver with closure in the usual manner.

Microscopical sections. There is relatively little necrosis of the liver cells in the very center of each liver lobule, but a great deal of fatty degeneration affecting the central ⅔ of each lobule. The liver cells are filled with large and small fat droplets and are extensively damaged. There are many polymorphonuclear leucocytes invading these areas.

Jan. 28-30. Animal recovering slowly.

Feb. 17. Dog is quite well and weighs 21 lbs.

Dog Q. Large Mongrel, Female, Weight 21½ lbs.
Dec. 3. *Chloroform Anæsthesia.*

Date.	Urine.	Reaction.	Alb.	Reducing bodies.	Cammidge test.	Remarks.
Dec. 4	Cage.	Acid.	Tr.	—	+	
Dec. 5	Cage.	Acid.	Tr.	—	+	
Dec. 6	Cage.	Acid.	Tr.	—	+	
Dec. 6	Death. Chloroform poisoning.					

Dec. 3, 2 p. m. *Chloroform anæsthesia* for *2¼ hours*. 1 oz. of chloroform given. Muscular tremors were marked during the anæsthesia. At the end of this period the animal was bled 120 cc. of blood and 150 cc. of normal saline infused. The animal recovered rapidly after the anæsthesia and seemed in good shape.

Dec. 4. Animal seems well. There is no vomiting.

Dec. 5. Dog is quiet but seems pretty well. *Operation* through

right rectus and removal of a wedge-shaped piece of liver. The wound is closed as usual.

Microscopical section shows every lobule to be extensively damaged. The central half shows almost complete hyaline necrosis with invasion by many wandering cells. The middle zone of liver cells shows many large fat droplets. The animal bled to death that night.

Dec. 6. Autopsy. The abdominal cavity contains a large amount of fluid blood. The surfaces are smooth. Thorax, heart, lungs, spleen and gastro-intestinal tract are all normal. *Pancreas* is very pale. The lobulation is uniform. There are no necroses nor hemorrhages.

The *liver* presents the usual appearance seen in chloroform poisoning. The centers of the lobules are very conspicuous, bright red, and the margins are swollen, opaque and yellowish. The capsule is tense, and the tissue is very friable.

Microscopical section. The spleen, kidney, and pancreas are quite normal. The liver shows practically the same condition described above.

Dog R. Small Fox Terrier, Female, Weight 10 lbs.
Dec. 3. *Chloroform Serum (Dog Q) Injected Intravenously.*

Date.	Urine.	Reaction.	Alb.	Reducing bodies.	Cammidge test.	Remarks.
Dec. 4	Cath.	Acid.	Tr.	—	+	
Dec. 5	Operation. Removal of piece of liver. Normal microscopically.					
Dec. 6	Cath.	Acid.	—	—	+	
Dec. 11	Cath.	Acid.	—	—	+	

Dec. 3. The blood obtained from dog Q was defibrinated, filtered through gauze, centrifuged and 50 cc. of clear serum obtained with aseptic precautions. Under ether anæsthesia dog R was bled 50 cc. from the jugular, and the 50 cc. of blood serum from dog Q was given intravenously. Dog R was under anæsthesia 30 minutes and recovered rapidly with no apparent ill effects.

Dec. 4. Animal is quite well. Urine is normal.

Dec. 5. Animal appears perfectly well. *Operation* through the right rectus with removal of a small, wedge-shaped piece of liver.

Microscopical section. There is absolutely no liver necrosis. The liver cells contain no fat droplets nor do they show any evidence of injury. There is an apparent increase in polymorphonuclear leucocytes in the capillaries in various parts of the liver lobules. Occasionally many of them will be found in the periportal tissue, but there is no regular distribution and no remarkable increase in number.

Dec. 6. Dog is active and quite well, and appetite good.

Dec. 12. Dog is healthy and wound is granulating.

Dec. 13-14. Animal is quite well.

Dec. 16. Dog put out in the yard.

Dog S. Large Mongrel, Female, Weight 34 lbs.
Chloroform Anæsthesia and Saline Injection.

Date.	Urine.	Reaction.	Alb.	Reducing bodies.	Cammidge test.	Remarks.
Dec. 17	Chloroform anæsthesia 2½ hours. Bled 280 cc. Infusion intravenously 500 cc. saline.					
Dec. 18	Cage.	Alk.	Tr.	—	+	
Dec. 19	Cage.	Alk.	+	—	+	
Dec. 19	Operation. Removal of piece of liver. Chloroform necrosis.					
Dec. 20	Cage.	Alk.	+	—	+	
Dec. 20	Animal bled to death. Chloroform poisoning.					

Dog S. Dec. 17. *Chloroform anæsthesia* for *2½ hours*, 1½ oz. of chloroform given. At the end of two hours the animal was bled 280 cc. from the jugular and infused intravenously with 500 cc. of normal saline.

Dec. 18. Animal feels pretty well and has passed a large amount of pale urine.

Dec. 19. No vomiting, appetite good. Dog pretty active. *Operation* through right rectus with removal of a wedge-shaped piece of liver.

Microscopical sections. Every liver lobule shows extreme central hyaline necrosis affecting at least ⅗ of the liver cells and great numbers of wandering cells have invaded these areas of necrosis. There is a thin middle zone of fatty liver cells and a thin rim of well-preserved liver cells about the portal spaces. Mitotic figures are numerous here. At operation the bleeding was very difficult or impossible to control, and it was thought that the animal might die from hemorrhage due to inefficient blood coagulation.

Dec. 20. Animal found dead in cage. *Autopsy.* The peritoneal cavity is full of fluid blood and no clots can be found anywhere. The organs in general are negative. The *pancreas* is absolutely normal. The liver shows the usual picture found in chloroform poisoning.

Dog T. Small Female Pup, Weight 12 lbs.
Chloroform Serum Injection.

Date.	Urine.	Reaction.	Alb.	Reducing bodies.	Cammidge test.	Remarks.
Dec. 17	Serum (120 cc.) from Dog S injected intravenously after bleeding 55 cc. under ether.					
Dec. 19	Cage.	Acid.	—	—	+	Small crystals.
Dec. 19	Cage.	Acid.	—	—	—	Coarse insoluble crystals.
Dec. 19	Operation. Removal of piece of liver. Normal.					
Dec. 20	Cage.	Acid.	—	—	+	Many typical crystals.

Dog T. Dec. 17. 280 cc. of blood obtained from dog S in a sterile manner were defibrinated, centrifuged and 120 cc. of clear blood serum obtained. Dog T was bled 55 cc. from jugular under ether anæsthesia and infused intravenously with 120 cc. of blood serum from dog S. Ether anæsthesia for 15 minutes. Animal recovered rapidly and appears quite well.

Dec. 18. Animal is quite well.

Dec. 19. Dog is well. Urine is pretty high colored and contains indican. Cammidge positive from one specimen of urine and negative in another during this same day. *Operation* through right rectus and removal of wedge-shaped piece of liver. Wound closed in the usual manner.

Microscopical section. The liver presents a normal picture in every respect. There are no fat deposits in any of the liver cells and no evidence of necrosis. Evidently the injection of this large amount of serum from an animal poisoned with chloroform had no ill effects.

Dec. 21-25. Dog recovering rapidly from the operation.

Dog O. Male Pup, Weight 14 lbs.
Nov. 12. *Chloroform Anæsthesia—Bleeding and Saline Infusion.*

Date.	Urine.	Reaction.	Alb.	Reducing bodies.	Cammidge test.	Remarks.
Nov. 14	Cath.	Acid.	—	—	—	Urine from bladder at autopsy.
Nov. 14	Autopsy. Little liver necrosis but central fatty degeneration. Pancreas normal.					

Dog O. Nov. 12. *Chloroform anæsthesia* for *2 hours*, ¾ ounce of chloroform used. After the first hour of anæsthesia the animal was bled 50 cc. from the jugular and infused intravenously 75 cc. of normal saline.

Nov. 13. Animal is quite well, no vomiting.

Nov. 14. Some bleeding from vessels of neck. Animal is killed with ether.

Autopsy. The viscera are negative except the liver. The *pancreas* is quite normal in gross and in microscopical sections.

Liver is large and swollen. The lobulations are conspicuous, and the centers are opaque and yellowish.

Microscopical sections. The liver lobules are relatively little affected. In the centers of the lobules one finds a few necrotic liver cells associated with many polymorphonuclear leucocytes. The central half of each lobule shows a large amount of fatty degeneration, and the cells contain large and small fat droplets.

Dog P. Fox Terrier, Male, Weight 14 lbs.
Nov. 19. *Chloroform Anæsthesia—Bleeding and Saline Infusion.*

Date.	Urine.	Reaction.	Alb.	Reducing bodies.	Cammidge test.	Remarks.
Nov. 20	Cage.	Acid.	+	—	+	
Nov. 21	Cath.	Acid.	+	—	+	Urine from bladder at autopsy.
	Autopsy. Little liver necrosis but much central fatty degeneration. Pancreas normal.					

Dog P. Nov. 19. *Chloroform anæsthesia* for *2 hours*, ½ oz. of chloroform used. During the last 15 minutes of anæsthesia the animal was bled 70 cc. from the jugular and infused intravenously with 90 cc. of normal saline.

Nov. 20. Animal seems pretty well, no vomiting.

Nov. 21. Animal killed by ether and bleeding from the carotids.

Autopsy. The viscera are negative except the liver. The *pancreas* is normal in every way in gross and microscopically.

Liver is larger than normal. The lobulations are sharply marked out. The central portions of the lobules are opaque. There is no evidence of necrosis. Microscopical section shows the central half of each liver lobule to be somewhat injured as indicated by fatty degeneration of the liver cells, but there is no conspicuous necrosis. A few polymorphonuclear cells are present in this region. but the liver is relatively little injured.

These experiments with with chloroform poisoning were all done in connection with other problems and the observations on the urine are somewhat fragmentary as a result, but we believe of considerable interest and importance. In these experiments the Cammidge test is almost constantly present and often more strikingly positive than in cases of pancreatitis, yet the autopsies show the pancreas to be normal. There is more or less cell injury and destruction with the appearance of great numbers of polymorphonuclear leucocytes in the liver lobules. The result of injecting pure chloroform into the portal vein is the production of scattered areas of necrosis, large and small, in all parts of the liver. The distribution is not uniform and the necroses are usually associated with periphery of the liver lobule and the portal structures. The cell reaction is practically the same here as in chloroform poisoning and there is autolysis of great numbers of degenerated cells, both liver cells and various wandering cells from the blood. The products of this cell injury and solution must appear in the blood as they are removed rapidly from the liver and we hope in another communication to bring evidence of this escape into the blood. It is probable, or almost certain, that some of these substances escape from the blood through the kidneys and appear in the urine—for example the ferment lipase and bile pigments. Possibly the substance or substances which give the Cammidge test may appear in the urine in the same way and surely are dependent upon the liver injury as this is the only constant pathological lesion in these experimental animals. It seemed possible to cause cell destruction and disintegration by artificial means—hydrolysis with acids—to investigate whether such materials introduced into the serous cavities could cause the appearance of the Cammidge test in the urine and such was found to be the case.

PNEUMONIA.

Dog 52. Mongrel, female, weight 14¾ lbs.

Oct. 11. Chloroform anæsthesia 1½ hours. 1 oz. of chloroform given.

Oct. 13. Operation and removal of piece of liver for microscopical examination. The liver presents the usual appearance. The center of each liver lobule shows hyaline necrosis of the characteristic type.

Oct. 21. Chloroform anæsthesia for 1½ hours. ¾ of an ounce of chloroform given.

Nov. 2. Dog has completely recovered and is put in the yard.

Nov. 8. Animal has distemper with considerable discharge from nose and eyes.

Nov. 12. Animal is quite sick and is placed in the cage for observation.

Nov. 13. Animal is losing ground.

Nov. 14. Animal is very sick, and there are muscular twitchings, Dyspnœa is quite marked. Urine obtained from cage shows no bile-pigment nor albumen, but a very typical Cammidge test.

Chart 52.

Date.	Urine.	Reaction.	Alb.	Reducing bodies.	Cammidge test.	Remarks.
Nov. 14	Cage.	Acid.	—	—	++	Typical and abundant Cammidge crystals.
Nov. 15	Cath.	Acid.	Tr.	—	+	

Nov. 15. Animal is having convulsions and is killed with ether.

Autopsy. The serous cavities, heart, spleen, gastro-intestinal tract are all normal.

Lungs. The bronchi in the lower lobes are slightly dilated and full of muco-purulent material. The posterior portions of the lungs are very œdematous and heavy, and there are scattered areas of consolidation. These areas of bronchopneumonia have a greenish, gray translucence. Some of them measure 2 cm. in diameter. This is the usual finding in fatal cases of distemper in the animals at the laboratory.

Microscopical section shows great numbers of polymorphonuclear leucocytes, but very little fibrin in the alveoli. The bronchi contain a similar exudate.

Kidneys show a few gray streaks and nodules in the cortex which under the microscope prove to be cellular scars, in some instances extending through the cortex. There are a good many casts in these areas and much distortion of the gland elements. *Pancreas* appears normal in gross, but under the microscope one finds a few very small focal necroses. They correspond to those found in human cases. The acini in these areas have partly disappeared and are replaced by connective tissue and wandering cells. These areas are not numerous nor of large size. The pancreatic acini as a rule are quite normal.

Liver. The lobulations and consistence are normal. There is an old scar at the site of the previous operation.

Microscopical sections show practically complete repair of the chloroform necrosis. The lobules are of normal size and practi-

cally all of the liver cells of normal appearance. There are a few pigmented phagocytes in the very centers of some of the lobules, all that remains of the repair which followed the chloroform necrosis. The bile ducts and the connective tissue are quite normal.

Hydrolytic Products Injected into Animals.

When it was found that animals suffering from pneumonia and chloroform poisoning gave a positive Cammidge test—in fact often a more abundant deposit of crystals than animals suffering from acute pancreatitis—it was suspected that cell destruction was a contributing factor. In order to try out this supposition, we hydrolyzed various tissues with acids—parts of pneumonic consolidation in dogs and man, thymus gland—neutralized the material and injected the clear filtrates into the peritoneal cavities of dogs. This procedure, as a rule, caused substances to appear in the animal's urine which gave the Cammidge test and these experiments afford strong evidence that the Cammidge reaction cannot be looked upon as a specific test for pancreatitis. The histories of these experiments are given in detail below.

Dog 61. Mongrel, Female, Weight 14¼ lbs.

Date.	Urine.	Reaction.	Alb.	Reducing bodies.	Cammidge test.	Remarks.
Nov. 23	Cath.	Acid.	—	—	—	Before injection.
Nov. 23	Injection of hydrolytic products of pneumonic lung.					
Nov. 24	Cath.	Acid.	—	—	+	Large amount of typical crystals.
Nov. 26	Cath.	Acid.	—	—	+	
Nov 27	Cage.	Acid.	—	—	+	Few crystals.
Nov. 28	Cage.	Neutral.	—	—	+	
Nov. 29	Cage.	Alk.	Tr.	—	+	
Nov. 30	Cage.	Alk.	Tr.	—	+	
Dec. 1	Cage.	Alk.	Tr.	—	+	Large amount of typical crystals.
Dec. 6	Cath.	Acid.	—	—	+	
Dec. 7	Operation. Pancreas quite normal. Lower arm ligated.					
Dec. 13	Cage.	Alk.	Tr.	—	+	
Dec. 17	Cage.	Acid.	—	—	±	Two types of crystals, one coarse, other fine, but both slowly soluble.
Dec. 19	Cage.	Acid.	—	—	+	Few small crystals.
Dec. 23	Cage.	Acid.	—	—	+	
May 1	Cath.	Acid.	—	—	+	Many typical crystals.
May 1	Melting point of these purified crystals 172° C.					

The *hydrolytic products* used in this experiment were obtained from dog 71 which died with a massive bronchopneumonia. Fifteen grams of this pneumonic consolidation were ground up and hydrolized for 2 to 3 hours with 200 cc. of 5 per cent sulphuric acid, the mixture being heated over a boiling water bath with a funnel as a condenser. At the end of this time the mixture was carefully neutralized with barium hydroxide after cooling. The clear filtrate was sterilized and used for experiment.

Dog 61. Nov. 23. Urine was obtained by catheter before the injection and found to give a negative Cammidge test. Under ether anæsthesia 65 cc. of the clear neutral filtrate (Dog 71) were injected slowly into the peritoneal cavity. The animal recovered rapidly from the anæsthesia.

Nov. 24. Animal is a little dull and has vomited.

Nov. 26. Dog looks quite well and is active as usual.

Nov. 27-Dec. 6. Appetite good. Animal active and very noisy.

Dec. 7 *Operation* and exploratory laparotomy. Digestion is going on rapidly and the lymphatics in the mesentery are dilated with milky fluid. The peritoneal cavity everywhere is normal. There are no adhesions. The *pancreas* is absolutely *normal.* It has a delicate grayish pink tint due to active digestion. Ligatures were passed around the lower arm of the pancreas close to its duodenal attachment, tied tightly, and the gland cut between them. This procedure isolated the distal portion of the lower arm of the pancreas and was done in connection with other work in progress. This piece of pancreas will undergo extensive atrophy and chronic induration.

Dec. 9-13. Animal is doing well.

Dec. 14-17. Animal is quite well, weight 11 lbs.

Jan. 25. Animal has regained weight (14½ lbs.) and is quite normal.

May 21. Animal has gained weight and is in perfect health.

Dog 77. Small Fox Terrier, Female, Weight 9½ lbs.

Date.	Urine.	Reaction.	Alb.	Reducing bodies.	Cammidge test.	Remarks.
Dec. 10	Cage.	Acid.	—	—	—	Before injection.
Dec. 10	Injection of hydrolytic products of thymus gland.					
Dec. 11	Cage.	Acid.	—	—	+	
Dec. 12	Cage.	Acid.	—	—	+	Typical crystals.
Dec. 17	Cage.	Acid.	—	—	+	
Dec. 19	Cage.	Acid.	—	—	±	Atypical burs of very fine crystals soluble with difficulty.
Dec. 25	Cage.	Acid.	—	—	—	Coarse insoluble crystals.
Dec. 29	Cage.	Acid.	—	—	—	
Feb. 7	Cage.	Acid.	+	—	—	Abundant amorphous deposit.

Hydrolytic products. The thymus gland from dog 71, weight 11 grams, was ground up and hydrolized with 100 cc. of 10 per cent sulphuric acid for 2 to 3 hours on water bath. The mixture was carefully neutralized with barium hydroxide, filtered, evaporated and concentrated to a volume of 80 cc. This clear filtrate had a pale amber color.

Dog 77. Dec. 10, 3 p. m. Intraperitoneal injection of 25 cc. of the material described above. Ether anæsthesia for 10 minutes. The urine obtained by catheter before this injection gave a negative Cammidge test.

Dec. 11. Animal appears rather sick.

Dec. 12. Animal is quiet and remains curled up in the cage.

Dec. 16. Animal is rather quiet, but seems normal.

Dec. 17. Animal, weight 10½ lbs., appetite good.

Dec. 29. Animal is well and weighs 11 lbs.

Jan. 25. Weight 12½ lbs.

Feb. 8. Animal is quite well and used for chloroform experiment.

Feb. 9. Animal dead. *Autopsy* at once. Viscera are of no particular interest. The pancreas is normal in every respect.

Hydrolytic Products.—The material obtained from the *thymus* gland is the same as that used in dog 77 and described there. *Pneumonic lung,* autopsy 3336. This was a human case showing massive grey hepatization. The material was obtained 17 hours after death. 250 grams of this material were cut up into small pieces and hydrolized on a boiling water bath for 7 hours with 1000 cc. of 5 per cent sulphuric acid. At the end of this time the greater part of

DOG 76. MONGREL, FOX TERRIER, FEMALE. WEIGHT 16¼ LBS.

Date.	Urine.	Reaction.	Alb.	Reducing bodies.	Cammidge test.	Remarks.
Dec. 6	Floor.	Acid.	—	(?)	+	
Dec. 7	Injection of hydrolytic products of thymus gland.					
Dec. 11	Floor.	Acid ?	—	—	+	
Dec. 13	Cage.	Neutral.	—	—	+	
Dec. 17	Cage.	Acid.	—	—	—	Amorphous deposit.
Dec. 22	Cage.	Acid.	—	—	+	Typical crystals.
Dec. 27	Hemolysis and resultant bile pigments in urine.					
Dec. 28	Cath.	Neutral.		(?)	—	Amorphous sediment.
Feb. 14	Cage.	Neutral.	—	..	+	Before injection.
Feb. 14	Injection of hydrolytic products of pneumonic lung.					
Feb. 15	Cage.	Faintly acid.	Tr.		+++	Enormous amount of typical Cammidge crystals in sheaves, soluble on contact with acid.
Feb. 16	Cage.	Faintly acid.	—		++	Same type of crystals.
Feb. 17	Cage.	Faintly acid.	—	—	+	Same type of crystals.
Feb. 19	Cage.	Faintly acid.	—	—	+	Same type of crystals.
Feb. 23	Cath.	Faintly acid.	—	—	—	Fine crystals in burs, soluble in 3 minutes.

the material was in solution. The mixture was neutralized with great care with barium hydroxide, filtered and concentrated to a volume of 500 cc., each cubic centimeter of this solution containing the extractives and cleavage products from ½ gram of lung tissue. The material obtained was a clear whiskey colored fluid which was sterilized and preserved for further use. The *Cammidge test* performed on this material shortly before injection gave a beautiful test. Great numbers of crystals appeared in the test tube. These crystals were very delicate and hair-like, arranged in sheaves and dissolved immediately on contact with acid. Several weeks later the same material after repeated sterilizations was again examined and the Cammidge test by the same worker was negative. A large amount of amorphous material came down in the test tube but no crystals.

Dog 76. Dec. 6. Animal is active and in heat.

Dec. 7. Ether anæsthesia and intraperitoneal injection of 25 cc. of the hydrolytic products from the thymus gland described above (Dog 76).

Dec. 12. Dog is active and quite well.

Dec. 27. Ether anæsthesia and injection intraperitoneally of 30 cc. of red blood corpuscles obtained by centrifuging some defibrinated blood from a normal animal.

Dec. 28. Animal is quite active and appears perfectly normal. Appetite good. *Urine* has typical appearance of "black-water." A granular brown sediment settles on standing. Test for bile-pigments are very positive. Albumen is abundant. No sugar. Cammidge test is quite negative.

Dec. 29. Urine is clearing up, but still gives test for bile pigment.

Jan. 25. Animal is quite well, weighs 18½ lbs.

Feb. 14. Dog is quite well. Ether anæsthesia and intraperitoneal injection of 20 cc. of *hydrolytic products* from the human *pneumonic lung* described above. Animal recovered rapidly from anæsthetic, but in the afternoon appears quite sick. There is a remarkable dyspnœa and vomiting. The animal appears fatally poisoned.

Feb. 15. The dog is quite well.

March 4. Animal is normal, weighs 18½ lbs.

May. Animal is normal and used for another experiment. The pancreas was resected. The gland was found to be normal in every respect.

DOG 80. FOX TERRIER, FEMALE, WEIGHT 16 LBS.

Date.	Urine.	Reaction.	Alb.	Reducing bodies.	Cammidge test.	Remarks.
Dec. 17	Cage.	Acid.	—	—	—	
Dec. 20	Cage.	Acid.	—	—	+	Few typical crystals.
Dec. 21	Cage.	Acid.	—	—	+	Few typical crystals.
Dec. 21	Cath.	Acid.	—	—	±	Atypical crystals.
Dec. 23	Cath.	Acid.	—	—	+	
Dec. 24	Cath.	Acid.	—	—	+	
Dec. 27	Cath.	Acid.	—	-	±	Few coarse insoluble crystals, modified by recrystallization.
Jan. 11	Cage.	Acid.	—	—	—	
Jan. 12	Cage.	Acid.	—	—	—	Milk diet.
Jan. 13	Cage.	Acid.	Tr.	+	—	Varying amounts of atypical crystals, usually in bur form and very resistant to acid.
Jan. 14	Cage.	Acid.	+	+	—	
Jan. 16	Cage.	Acid.	+	+	—	
Jan. 17	Cage.	Acid.	Tr.	++	—	
Feb. 24	Cath.	Acid.	—	—	—	Before injection.
Feb. 24	Injection of hydrolytic products of pneumonic lung (10 cc.).					
Feb. 24	Cage.	Acid.	—	—	—	3 hours after injection.
Feb. 24	Cath.	Acid.	Tr.	—	—	6 hours after injection.
Feb. 25	Cath.	Acid.	Tr.	—	—	
Mch. 2	Cath.	Acid.	—	—	—	Before injection.
Mch. 2	Injection of hydrolytic products of pneumonic lung (17 cc.).					
Mch. 2	Cage.	Faintly acid.	—	—	+	2½ hours after injection.
Mch. 3	Cath.	Faintly acid.	—	—	+	Few crystals.
Mch. 3	Cage.	Faintly acid.	—	—	+	Typical crystals.

Dog 80. Dec. 17-27. Animal is normal in every respect. The catheterized urine on this last day (Dec. 27) gave a very unsatisfactory Cammidge test. After standing 24 hours a few coarse, insoluble crystals came down, but after dissolving again by boiling and filtering, a different type of crystal was formed which dissolved readily. It would seem that a slight change in concentration or in rapidity of cooling had modified the type of crystal to such an extent as to modify its solubility, a point upon which Cammidge lays much emphasis.

Jan. 11-16. Animal is quite well, and is on a strict milk diet, about 750 cc. given daily.

Jan. 25. Animal weighs 20 lbs., and is in excellent health.

Feb. 24. Under ether anæsthesia 10 cc. of the hydrolytic products from the pneumonic lung described above (dog 76) were injected intraperitoneally. Repeated observations during this period before and after the injection gave a negative Cammidge test.

March 2. Under ether anæsthesia the animal was given intraperitoneally 17 cc. of the same solution obtained from the pneumonic lung. Before the injection the urine was negative, but repeated examinations after the injection gave positive Cammidge tests (see chart). The animal appeared pretty sick in the afternoon.

March 3. Animal is quite well and lively as usual.

March 17. Dog is quite well, weighs 21¾ lbs.

Nov. 8. Operation through right rectus: common bile duct doubly ligated and cut between ligatures.

Nov. 9. Bile pigments are present in the urine.

Nov. 10. Urine is high colored and contains a large amount of bile pigment.

JAUNDICE.

Dog 69. Fox Terrier, Female, Weight 13¼ lbs.
Nov. 8. *Ligation of Common Duct.*

Date.	Urine.	Reac-tion.	Alb.	Reduc-ing bodies.	Cam-midge test.	Remarks.
Nov. 10	Cage.	Acid.	—	—	+	
Nov. 12	Cage.	Acid.	Tr.	+	—	
Nov. 15	Cath.	Acid.	Tr.	—	—	

Nov. 14. Animal showed the clinical picture of obstructive jaundice, clay-colored stools, high colored urine, icteroid tint of sclerotics.

Nov. 16. Progressive loss of weight—12 lbs.

Nov. 26. Autopsy. All the tissues are deeply bile-stained. Otherwise the viscera are of slight interest. The pancreas is quite normal. The gall ducts and gall bladder are enormously dilated and the liver is a very deep greenish yellow color.

NORMAL DOGS.

Dog 78. Small mongrel, female, weight 13 lbs. This animal had been pregnant about 3 weeks previously and has nursed her pups for 2 weeks. At this time the breasts are decidedly prominent, and the animal is in excellent health.

Date.	Urine.	Reac-tion.	Alb.	Reduc-ing bodies.	Cam-midge test.	Remarks.
Dec. 12	Cage.	(?)	—	—	+	Many typical slender crystals.
Dec. 13	Cage.	Acid.	—	—	+	Small crystals.
Dec. 17	Cage.	Acid.	—	—	+	

Dec. 12-13. The animal is in perfect health. Indican was present in the urine, but no bile-pigments. The urine is decidedly concentrated and high colored.

Jan. 8. Animal is in good health and used for an experiment in metabolism.

Dog 93. Small mongrel, female, weight 12½ lbs. The animal is normal in every respect and appetite good.

Date.	Urine.	Reac-tion.	Alb.	Reduc-ing bodies.	Cam-midge test.	Remarks.
Feb. 22	Cath.	Acid.	—	—	+	Two types of crystals, one type very fine hair-like crystals in sheath form, the other considerably larger and more like the typical Cammidge crystals; both soluble in acid.
Feb. 23	Cath.	Acid.	—	—	+	

March 4. Animal is in perfect health and used for experiments in metabolism.

HUMAN CASES.

Blake: Autopsy 3298. This case was clinically one of acute pancreatitis following an operation for gall-stones.

Date.	Urine.	Reac-tion.	Alb.	Reduc-ing bodies.	Cam-midge test.	Remarks.
Nov. 18	Mixed.	Alk.	Tr.	—	+	Large amount of typical crystals.
Nov. 19	Mixed.	Acid.	(?)	—	++	
Nov. 20	Mixed.	Alk.	Tr.	—	+	Few crystals.

Autopsy Nov. 21. Anatomical Diagnosis: Icterus; chronic cholecystitis and cholangitis; operation wounds (choledochostomy); abscesses in pancreas and lesser omental cavity; acute pancreatitis with fat necroses; acute general peritonitis; acute gastritis and diphtheritic enteritis; subacute nephritis; bronchopneumonia and œdema of lungs; chronic splenic tumor.

The abscess cavity had caused digestion and disappearance of the greater part of the body of the pancreas, the main pancreatic duct, however, persisting with an intact lumen. The head and tail of the organ showed a subacute type of inflammation. Here the gland was hard, firm, enlarged and speckled over with little fat necroses.

Microscopical sections. The pancreas shows an extreme grade of chronic induration. There are many fat necroses; some of them are partly calcified, while others are quite recent, and surrounded by fragmented nuclei.

Stauffer. Autopsy 3320. Clinically this case was one of very acute leukæmia of two months duration. There was progressive anemia and slight increase in white blood cells from 8000 to 13,000. Differential counts showed from 50 to 70 per cent of large undifferentiated mononuclear cells.

Date.	Urine.	Reac-tion.	Alb.	Reduc-ing bodies.	Cam-midge test.	Remarks.
Dec. 27	Mixed.	Acid.	(?)	—	++	Beautiful needle-like crystals, easily soluble.
Dec. 29	Mixed.	Acid.	—	—	+	
Jan. 3	Mixed.	Acid.	(?)	+	—	

Jan. 3. Autopsy 3320. Anatomical Diagnosis: Leukæmia (myeloid); hyperplasia of bone-marrow and lymph glands; splenic tumor; anemia; fatty degeneration of myocardium and liver; pigmentation of liver, portal glands and testicles; disseminated ecchymoses; hemorrhagic bronchopneumonia and œdema of lungs; acute fibrinous pleurisy; subacute adhesive pericarditis.

The viscera showed the usual findings in this condition. The *pancreas* is of normal size and general appearance. The lobulation clean cut. Section shows no abnormality.

Microscopical section. The stroma is little increased in amount, but the gland elements are quite normal. This is practically a normal gland as regards acini, islands of Langerhans and collecting ducts.

Several other cases in the wards were examined but are not reported because of the lack of autopsy reports. One of the workers in this group who has tested his own urine repeatedly has found on many occasions a typical positive Cammidge test, yet he is a strong adult male with excellent past history and not the slightest evidence of any pancreatic disease.

General Discussion.

Work in this laboratory has convinced us that there are several sources of error in the method—test " C "—and that the personal interpretations of a given test may be various. We have endeavored to eliminate this personal factor by duplicate tests and by repeated examinations of crystals from a single specimen by various workers on the same or different days. Even when quite inconspicuous the sediment in any given tube should be examined under the microscope, for it may be very slight and yet contain typical crystals. The crystals vary in the most amazing degree in some experiments, and it is not unusual to find at least two distinct types of crystals, perhaps both insoluble or both readily soluble in acid or one readily soluble and the other resistant to the acid. In such cases it is easy to understand how one person could diagnose the test as positive and a less enthusiastic observer

as negative. Parallel tests on the same specimen of urine by different workers usually gave identical results, but sometimes there were some minor differences in the shape and solubility of the crystals. It was found that the crystals could be modified to a considerable degree by slight changes in concentration of the solution or rapidity of cooling. When it was further noted that the solubility of these same crystals could vary to a certain degree depending on their shape and size, it seemed certain that this might be a grave source of error. The solubility depends in part upon the delicacy of the crystals—the long slender blade forms being almost invariably soluble on contact with acid. Changing the salt content may modify the type of the crystals and certainly the amount. This may be of importance when a concentrated urine is being tested.

It seems pretty clear from various publications that different observers are dealing with different substances or combinations of substances. The melting point of the Cammidge crystals is given as all the way from 140° to 180°. It is difficult to obtain a mass of these crystals in pure form, free from salts, etc., but this factor alone cannot explain the great variations seen in the publications of various workers. Our observations have not been extensive on this point, but are of interest because both series of determinations were made by the same worker under the same conditions. The pure crystals were obtained from two different animals—dog 72—subacute pancreatitis and dog 61—slight pancreatic atrophy and induration. The crystals were purified by repeated recrystallizations and washings in distilled water until the type of crystal was constant and no amorphous material was present. The material was thoroughly dried and the melting point determined by repeated observations. Crystals from dog 72 melted at 153-154° C. but those from dog 61 melted at 172° C. We are not prepared to explain these observations, but give them for what they are worth. We have made no observations on crystals obtained from human cases, but Cammidge claims that the crystals from both sources are identical and melt sharply at a fixed temperature 178-80° C. We are unable to confirm his observations.

A review of our experiments on acute and chronic pancreatitis shows an uncertain state of affairs as far as the Cammidge test is concerned. We believe that the pathological lesions produced by injection of bile into the pancreatic duct more closely resemble those found in human cases than do the lesions which follow crushing or ligating the gland as done by other workers. Our experience shows that such an acute process, if not too severe, will heal rapidly, and result in a chronic diffuse pancreatitis similar in all respects to the condition found in some human cases. Our experiments confirm the observations of most workers that the Cammidge test is usually present in the acute stage of pancreatitis, but even here it is not constant (dog 81). In the healing stage of the pancreatitis the Cammidge reaction is more often absent than present, and in advanced chronic pancreatitis it may be consistently absent (dog 84).

The test is not infrequently positive in normal dogs and men or may be present at one time and absent at another. The chart (dog 80) is very instructive showing how the test may vary in the same animal from week to week while the dog is in perfect health. It was suspected that the diet might have some influence on the test, but we have no evidence for this view. Two healthy animals which were under observation for a considerable period were placed on a fixed diet for 10 days—one on milk alone (dog 80) the other on raw meat alone (dog 84). The one on a milk diet (about 750 cc daily) developed abundant reducing bodies (lactose) in the urine, but the Cammidge test was negative in both animals during the period of observation.

Chloroform poisoning in dogs offers an opportunity to study the urinary changes following an extensive injury to the liver—advanced central liver necrosis and fatty degeneration. The pathological lesion is almost invariably limited to the liver, but in a few cases one finds a few fat necroses and opacities in the pancreas. The pathology of the disease has been described fully in a previous communication (chloroform poisoning—Whipple and Sperry). In a typical case at the end of 36 hours after chloroform anæsthesia, the liver is found to show central necrosis involving perhaps two-fifths of every liver lobule. This area of necrosis is invaded rapidly by wandering cells which help in the solution and removal of the tissue. This change is effected in great part during the next 3-5 days. During this time the products of cell autolysis are being removed by the blood stream and probably excreted at least in part by the kidneys. During this period the Cammidge test is almost constantly positive and the crystals may occur in enormous amounts. So it seems just to assume that the liver necrosis accompanied by the solution and absorption of the dead liver cells and degenerated leucocytes is responsible for the presence of the substance in the urine giving abundant Cammidge crystals.

Similarly one is not surprised by the reports of quite positive Cammidge tests in cases of pneumonia and peritonitis where there is much cell destruction and solution, particularly in the late stages. Only a single case of pneumonia in a dog has come under our observation, and that animal gave a typical Cammidge reaction. Some of the consolidated lung tissue from this animal which was very rich in polymorphonuclear leucocytes was hydrolized with acid, neutralized, filtered and concentrated to a clear amber fluid. It was thought that this could be looked upon as a rough imitation of the cell autolysis *in vivo*. Intraperitoneal injection of this fluid caused the substance to appear in the urine which gives the Cammidge test. Similar experiments were tried using hydrolyzed dog's thymus and human lung with constant results. Some of the animals were poisoned slightly by the injection, and it might be argued that the poisoning had upset the animal's metabolism and was responsible for the reaction—not necessarily any given substance in the injected fluid. It would be difficult to disprove this but the hydrolytic products themselves will give the Cammidge test when in proper dilution.

The two human cases are reported because they illustrate

two widely differing conditions in which cell destruction is active and perhaps explains the Cammidge test which was typical in both. The first case showed a large abscess pocket full of pus which had caused solution of nearly one-half of the pancreas, subacute pancreatitis and general peritonitis by direct extension. The second case of acute leukæmia we may assume showed rapid production and destruction of white blood cells. However, it is important to remember that perfectly normal vigorous men may give a positive Cammidge test on some occasions.

Conclusions.

1. The Cammidge test is of little value in establishing a diagnosis of acute pancreatitis in dogs. If the test is negative, it is pretty strong evidence against an acute pancreatitis.

2. The Cammidge test is of even less value in the condition of chronic pancreatitis in dogs and may be consistently absent even in extreme grades of this disease.

3. A positive Cammidge test is not infrequent in normal dogs and men.

4. The Cammidge test is almost constantly present in chloroform poisoning in dogs—a condition in which there is extensive liver necrosis and cell autolysis.

5. The Cammidge test may be present in cases of pneumonia or in any condition where there is active cell destruction and autolysis.

6. The Cammidge test may be produced experimentally almost at will by intraperitoneal injections of hydrolytic cleavage products. These split products may be prepared by boiling pneumonic lung tissue (dog or man) or thymus for hours with dilute acid, neutralizing, filtering and concentrating to a clear fluid.

7. The melting point of the crystals varies under different conditions indicating that the substance or substances are not constant.

8. The method is open to various errors and too much depends upon the personal equation, particularly in the interpretation of the various crystals.

9. The method is time consuming, and the results do not seem to warrant the expenditure of the time and materials.

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NOTES ON NEW BOOKS.

Les Problèmes de la Vie. Essai d'une interprétation scientifique des phénomènes vitaux. Par Dr. Ermanno Giglio-Tos. IVe Partie. La variation et l'origine des espèces. *(Cagliari: Chez l'auteur, à l'université, 1910.)*

This is a book which should be read and studied in association with the preceding parts, in which the author deals with vital phenomena from a theoretic and ideal point of view. In this volume he studies "the actions which may modify more or less profoundly the normal and ideal course of the fundamental biological phenomenon, and determines as exactly as possible the value of these actions, and the consequences which may be drawn from them." It is a work for the advanced biologist, and its importance can only be fully appreciated by one trained in special lines of research. The writer is a professor of zoology and comparative physiology in the University of Cagliari.

The Diseases of Infancy and Childhood, Designed for the Use of Students and Practitioners of Medicine. By Henry Koplik, M. D., etc. Third edition. Revised and enlarged. *(New York and Philadelphia: Lea & Febiger, 1910.)*

This book of 944 pages enjoys a well-merited popularity. The subject-matter is well arranged and on the whole the single chapters are rich in useful information. In his description of the methods of analysis of human milk, the author states that he utilized the method of Woodward for the determination of the proteids and found it satisfactory. The final step of this method involves the use of the centrifuge, reading there the volume of the precipitated proteid. As a rule such methods cannot be much relied upon for accuracy. We therefore should have liked to see the authors statement fortified by control analyses. Fortunately in this particular instance a far reaching accuracy is not necessary for practical purposes. In the chapter on Maternal Nursing the author states that he has found the mothers very anxious to perform this function, but the average mother to-day has not the physical development that fits her to nurse the child. To this statement propounded *ex cathedra* we must register our most serious exceptions. It appears to us that the fault is not to be found so much with the physical development of the mother as with the neglect with which the technique of nursing has been treated by the physicians, an objection from which this chapter is not free by any means. For instance the gradual change of the composition of the breast-milk during nursing, the fact that the infant takes the bulk of its food within the first minutes has not received sufficient attention. These factors frequently enter into consideration in the management of a case and in the collection of the milk for analysis. As usual the contraindications to maternal nursing are treated rather cavalierly while the possibilities of keeping the baby on the breast where the lactation is delayed or has become insufficient for some reason receive the scantest of attention. The dangers of milkstasis for the lactation should have been emphasized much more. The author relates that he has seen infants thriving in spite of suffering from repeated colic, while the milk showed quite a number of colostrum corpuscles. After certain hygienic hints were carried out by the mother these colostrum corpuscles disappeared from the milk, the colic abated and the infant returned to a normal condition. Very good; but is it not very much within the scope of a text-book to inform the student about these certain hints? With regard to the problem of the wet nurse it is stated: "In the first place it is not moral nor conducive to the future good of the race to ask a mother (the wet nurse) to put aside her own child and to deprive it of the breast for the sake of a strange child." There cannot be the slightest doubt that—as far as the physician is concerned—one baby is as good as another, but we fail to see the necessity of depriving the baby of the wet nurse of the breast. If a mother cannot or will not nurse her own baby it is best to provide a good wet nurse if possible. Any discussion of this question is impossible and under such conditions it is the duty of the physician to see to it that the baby of the wet nurse is not pushed aside. The artificial feeding of infants is treated in twenty-four pages. The author treats this subject in a conservative manner and his presentation is free from dogmatic statements. It may not be amiss giving a place to the very simple method described by Czerny and Keller among the more complicated methods. The following sentence is not clear: "The difficulty of calculating what is known as the calories necessary to the maintenance of nutrition and body weight—and by calories is meant the amount of albumin or proteids, fats, salts, and water mentioned above—is, that the physician cannot always have at his disposal a method by which these calculations can be made." In the determination of the caloric value of food the proteins, fats and carbohydrates enter in consideration, while the salt and the water do not.

The description of the allergic phenomena underlying the cutaneous tuberculin reaction is not clear. According to von Pirquet an organism infected with tuberculosis or having passed through such an infection possesses a certain antibody. This antibody reacts with the tuberculin and there results a toxic product, which is responsible for the reaction.

In the chapter on syphilis we miss any mention of the Wassermann-Bruck reaction.

Eleven pages are devoted to the diseases of the skin. We should like to see this section enlarged in a future edition and particularly the different tuberculous lesions of the skin may deserve a separate chapter here. The lesions due to rhus toxicodendron and their treatment should find a place here also.

Taking the book as a whole it is very serviceable and can be recommended strongly to the student as well as to the practitioner.

A System of Operative Surgery. By Various Authors. Edited by F. F. Burghard, M. S. (Lond.), F. R. C. S. (Eng.), etc. In Four Volumes. Vol. III. *(London: Henry Frowde and Hodder & Stoughton.) Oxford Medical Publications.*

This volume is divided into five Sections as follows:

Section I. Part 1. Operations for Tuberculous Disease of the Lymphatic Glands, by Harold J. Stiles. Part 2. Operations upon the Spleen, by B. G. S. Moynihan and Harold Upcolt. Part 3. Operations upon the Thyroid Gland, by James Berry.

Section II. Operations upon the Bile Passages and the Pancreas, by A. W. Mayo Robson.

Section III. Part 1. Operations upon the Skull and Brain, by L. Bathe Rawling. Part 2. Operations upon the Spinal Cord and Canal, by W. Thorburn.

Section IV. Part 1. Operations upon the Kidneys and Ureters, by David Newman. Part 2. Operations upon the Bladder, by J. W. Thomson Walker. Part 3. Operations for Vesical Calculus, by P. J. Freyer. Part 4. Operations upon the Prostate by P. J. Freyer. Part 5. Operations upon the Urethra, by J. W. Thomson Walker. Part 6. Operations upon the Male Genital Organs, by F. F. Burghard.

Section V. Part 1. Operations upon the Breast, by Harold J. Stiles. Part 2. Operations upon the Thoracic Wall and Its Contents, by Rickman J. Godlee.

The general excellence of this system will be best measured when it is complete, but like all systems this one suffers from an inequality in the value of the articles; and there is one special defect and that is a very incomplete index. To American students the work is of special interest in presenting the views of many of

the leading English operators and a comparison with prevalent American surgical methods and ideas is enlightening. A busy surgeon hardly has time to consult such a work as this, but he who has time to read will be glad to have this volume on his shelves for study and reference.

Précis du traitement des fractures par le massage et la mobilization. Par le Docteur Just Lucas-Championnière. Un vol. in-16 de 268 pages. Prix: 3 fr. 50. G. Steinheil, éditeur, 2, rue Casimir-Delavigne, Paris.

To all students of surgery the author's name is well known, as one of the leading surgeons in Paris. He has written other works on the cure of hernia, and aseptic surgery and the present small volume is a résumé of a larger work on the treatment of fractures. Those who enjoy reading French and desire to know what this surgeon thinks of the value of massage and mobilization of fractures will be glad to have this book which they can easily slip into their pocket. The author's experience and opinions deserve study and consideration.

La Cure radicale de la hernie inguinales. Leçons professées à l'Hôtel-Dieu. Par le Docteur Lucas-Championnière. (*Paris: G. Steinheil, éditeur, 1909.*)

Few surgeons have written more than this author on hernia, and as its radical cure is one of constant interest to surgeons, his last (?) word on the subject will be gladly received. There is an operation for hernia which bears his name and in which he has supreme confidence, but as there seems to be no one operation which is always successful, so this one cannot be recommended for every case. This small volume of less than 200 pages is well illustrated and printed, and those who cannot read French will miss a distinct pleasure in being unable to study this work at first hand.

The Harvey Lectures, 1908-1909. (*Philadelphia and London: J. B. Lippincott Company, 1910.*)

All these lectures with the exception of one on "Heredity in Man" by C. B. Davenport have been published in different medical journals since they were delivered, but as a token of the good work being done by the Harvey Society of New York, under whose auspices they were given, it is pleasing to have them collected in a volume. The society may be congratulated on the success of their undertaking, and the selection of the lecturers has been most happy. These are not popular lectures but intended rather for doctors; only one of them—but one of the best—being of a popular quality. It is the lecture by Prof. Calmette of Lille on "Intestinal Infection and Immunity in Tuberculosis," a brief but clear exposition of the problem. The other papers are more difficult of comprehension except to students working along certain lines. There is another paper by His on Immunity and one by Anderson and Rosenau on Anaphylaxis, and there are four papers directly or closely connected with metabolism. The three lectures by Lusk, Falta and Leathes should be read together, as Lusk and Falta discuss Diabetes from the side of metabolism and therapy respectively, and Leathes analyzes the destruction of fats by the liver. MacCallum's paper is entitled simply "Fever" but it is essentially a study of its various causes. The remaining lectures are by Macallum and Davenport and both deal with problems of heredity but from absolutely unallied standpoints. It is a pity that the lectures are not printed exactly as they were delivered. There is but a brief and therefore a most unsatisfying sketch of Davenport's paper, and Calmette's is undoubtedly shorter, while Anderson's and Rosenau's is longer than when delivered. Otherwise there is no criticism to be found with the lectures which with their varying interests will appeal to various classes. They are all well worth reading—even Davenport's.

Emergencies of General Practice. By Percy Sargent, M. B., F. R. C. S., etc., and Alfred E. Russell, M. D., F. R. C. P., etc. Price, \$5.50. (*London: Henry Frowde and Hodder & Stoughton, 1910.*) *Oxford Medical Publications.*

The authors have been to some pains to compile a work for which it is to be feared that there can be no wide demand, for the information contained in it should be ready to use in the brain of every student about to graduate in medicine. For the country practitioner to have such a volume to refer to from time to time may be serviceable, but the city practitioner will seldom have occasion to use it. It is difficult to know exactly how to define "emergency" and Sargent and Russell have stretched its real meaning liberally so as to include a large variety of conditions. There are chapters on wounds, hæmorrhage, burns, fracture, injuries to joints, acute infectious diseases, diseases and injuries of the chest, the abdomen, and the nervous system, etc. To those who enjoy a quiz compend and like to have information well condensed, this book can be recommended for it is well written and reliable.

Constipation and Allied Intestinal Disorders. By Arthur F. Hertz, M. A., M. D., Oxon., M. R. C. P., etc. (*London: Henry Frowde and Hodder & Stoughton, 1909.*) *Oxford Medical Publications.*

One cannot help being impressed by the thoroughness with which the author has dealt with the various phases of his subject.

But perhaps the most distinguishing feature of the work is the skillful use he has made of bismuth in diagnosing the different abdominal conditions. Indeed, the work might well have been called a "Study in Bismuth." Nearly every form of constipation known has been subjected to the bismuth X-ray diagnosis, with the result that several interesting and highly instructive plates have been obtained—such as those shown on page 102.

It is unfortunate, though, that all the drawings and reproductions are schematic, because one is apt to get the impression that a little bismuth and an X-ray plate are all the requirements necessary to reveal any old form of intestinal sluggishness or incompetence. The reverse is, of course, true—it requires an experienced eye to interpret even a good plate after a bismuth meal.

Taking the book as a whole, we would consider it suitable rather for reference than as a text-book or a book for the busy practitioner. It is well arranged, the style is good and the literature given at the close of each chapter is both voluminous and up-to-date. In addition to this, the author adds an appendix to the book in which he tells of "The Administration of Bismuth Salts for the Skiagraphic Examination of the Alimentary Canal." This, of itself, should prove to be of great value to those who wish to use or are accustomed to use bismuth and the X-ray in abdominal conditions.

B. W. B.

International Clinics. Edited by Henry W. Cattell, M. D. Volume II. Twentieth Series. (*Philadelphia and London: J. B. Lippincott Company, 1910.*)

An unusual and amusing contribution to this volume is Curtin's account of "The Book-Plates of Physicians, with Remarks on the Physician's Leisure-Hour 'Hobbies.'" There are numerous illustrations many of which show that strange and common desire on the part of doctors to indicate their profession by some evidence of death—like a skull or skeleton. Walsh's paper on "The Progress of Medicine During the Past Twenty Years" is good reading, and in "The Spontaneous Cure of Cancer," by McConnell, are records of some most remarkable cases. This article should be read in connection with Sherrill's on "Some Remarks Concerning So-Called Inoperable Tumors, etc." There are other papers on various subjects also well worth reading.

Progressive Medicine. Edited by Hobert Amory Hare, M. D., etc. Assisted by Leighton F. Appleman, M. D., etc. Volume II. June, 1910. (*Philadelphia and New York: Lea & Febiger, 1910.*)

In this volume the latest and most important contributions, as well as most recent views on hernia are reviewed by Coley; on surgery of the abdomen, exclusive of hernia, by Foote; on gynecology by Clark; on diseases of the blood, diathetic and metabolic diseases, diseases of the thyroid gland, nutrition, and the lymphatic system by Stengel; and on ophthalmology by Jackson. With the help of this work the general practitioner can keep himself well informed on the progress made in many branches. It is a pity that the editors do not pay more attention to systematizing the bibliography of the various chapters, the titles of various medical publications referred to should be abbreviated throughout in the same way, and references to volumes, pages, and dates should conform to one plan.

A Practical Treatise on Fractures and Dislocations. By Louis A. Stimson, B. A., M. D., LL. D. (Yale), etc. Sixth Edition, Revised and Enlarged. Illustrated. (*New York and Philadelphia: Lea & Febiger, 1910.*)

This excellent work is so well known by the profession that it needs no fresh commendation. Dr. Stimson has added to its value by new studies of injuries to the small bones of the wrist and ankle, and fractures of the acetabulum, femur, and dislocation of the jaw. The book is so complete that almost every known fracture and dislocation is described in it, and no surgeon can afford to be without this classic.

Diseases of the Colon and Their Surgical Treatment. By P. Lockhart Mummery, F. R. C. S., Eng., etc. Illustrated. Price, 10s. (*Bristol: John Wright & Sons, Ltd. London: Simpkin, Marshall, Hamilton, Kent & Co., Ltd.*)

Diseases of the entire gastro-intestinal tract require much more careful study than they have yet received, and this small volume which is "founded upon the Essay which was awarded the Jacksonian Prize for 1909 by the Royal College of Surgeons," is an addition to the subject which will help many a student. It treats the diseases from both a medical and surgical standpoint, and while in no sense exhaustive the author has succeeded in bringing out clearly the salient features of the different conditions described. On diagnosis he has laid especial stress, which after all is the most essential feature to secure good treatment; he has also carefully considered the effect of adhesions, which is not always sufficiently present in the mind of an operator, so that as a result of poor technique the patients' condition may be worse after an operation than before it, simply due to their development. To constipation, which is a condition too often neglected by the physician through indifference, Mummery has also given full attention, as well as to other common troubles of the colon. As far as the author goes, the work is excellent, and the publishers may also be commended for their part.

Manual of Operative Surgery. By John Fairbairn Binnie, A. M., C. M. (Aberdeen). Professor of Surgery, Kansas State University, Kansas City, etc. Volume II. Vascular System, Bones and Joints, Amputations. Fourth Edition, Revised and Enlarged with 550 Illustrations. (*Philadelphia: P. Blakiston's Son & Co., 1910.*)

In the preface the author says he has devoted an unusual proportion of the volume to a consideration of operations less frequently demanded, some of which are even still *sub judice*.

He states that the aim of this manual is particularly to give aid to the junior surgeon when he is brought face to face with the difficult or unusual in his practice.

The book is divided into 47 chapters and deals with the surgery of the Vascular system, Bones and Joints, Amputations, Tendons, and Dupuytren's Contracture. The chapter on Congenital Luxation of the Hip is written by G. G. Davis of Philadelphia.

The descriptions are necessarily brief, but convey the ideas admirably. The operative procedures are divided into steps, which are taken up in order.

There are a number of references scattered through the text and quotations from important papers.

The illustrations are good and the book is up-to-date. J. S. D.

Physiology and Pathology of the Semi-Circular Canal. Being an Excerpt of the Clinical Studies of Dr. Robert Barany with Notes and Addenda Gathered from the Vienna Clinics. By Adolph C. Ibershoff, M. D., and a Foreword by Royal S. Copeland, M. D. Price, $1. (*New York: Paul B. Hueber, 1910.*)

This is a book of comparatively few pages. It will serve, however, to place before the reader in available form some more recent clinical investigations of the inner ear which have, as yet, not found their way into the regular text-books. Several pages are devoted to the subject arbitrarily entitled "Caloric Nystagmus" and it would seem that a perusal of these pages should convince most otologists that these tests spoken of should be more generally adopted in the routine examination of many ear patients and if it does this the little book will serve the purpose for which it has been gotten up. B. B. B., Jr.

Errors of Refraction and Their Treatment. A Clinical Pocket-Book for Practitioners and Students. By Charles Blair, M. D., F. R. C. S. Second Edition. Price, 2s. 6p. (*Bristol: John Wright & Sons, Ltd. London: Simpkin, Marshall, Hamilton, Kent & Co., Ltd., 1910.*)

This is a very small book in which the most elementary principles regarding the refraction of the human eye are set forth. It is rather difficult to see for what class of readers this book is designed as all the facts therein stated are covered in one of the reliable text-books on the eye, which the medical student can readily get at, and the general reader who might be ambitious to learn something of this can find all these facts in any high-school physics or encyclopedia. The book is too elementary to be of value to advanced students of ophthalmology. B. B. B., Jr.

Education in Sexual Physiology and Hygiene. A Physician's Message. By Philip Zenner, Professor of Neurology in the Medical Department of the University of Cincinnati. Price, $1. (*Cincinnati: The Robert Clarke Company, 1910.*)

For those who have to teach these subjects this book may prove helpful, but is too brief to be more than suggestive along certain lines.

Diseases of the Eye. A Handbook of Ophthalmic Practice for Students and Practitioners. By G. C. de Schweinitz, A. M., M. D., etc. Illustrated. Sixth Edition. Thoroughly Revised. Price, $5. (*Philadelphia and London: W. B. Saunders Company, 1910.*)

We have always looked with favor on Dr. de Schweinitz's well-known book on the Diseases of the Eye. This is the sixth edition, which shows that it has met with merited approval from medical practitioners and students. But few changes are noted in the present edition, and we have no doubt but that it will continue to be the means by which many senior medical students of forthcoming years will acquire accurate and reliable information concerning the Diseases of the Eye. As a text-book for medical students the book has only one fault, prevalent throughout, and that is that

in regard to the therapeutic measures, the author is too liberal in his suggestions and not definite and dogmatic enough in his recommendations. However, the minor faults are few, and the spirit of conservatism in which it is written—for the author rides no hobbies of his own nor has he been carried away by those of others—commends it to all those interested in the study of eye diseases. B. B. B., Jr.

Transactions of National Conference on Pellagra, Held under Auspices of South Carolina State Board of Health at State Hospital for the Insane, Columbia, S. C., November 3 and 4, 1909. (*Columbia, S. C.: The State Co., Printers, 1910.*)

As the first collective report on pellagra in this country, these transactions are most important, and henceforth the recognition and diagnosis of the disease will be much easier for the general practitioner; and soon it will be possible to make a fair estimate as to its prevalence in the southern States. It is most necessary that individual cases should be recognized as early as possible, since only in the first stages does the disease seem to be curable, and its chronicity and later symptoms are much to be dreaded. Now that the medical profession is beginning to be aroused as to its prevalence, we may hope that its spread may be limited and that if necessary the U. S. government will take such steps as lies in its power to control it. In this report there are many admirable papers dealing with the clinical side of pellagra, and the interest of the conference was much enhanced by the presence of, and the reading of papers by foreign medical men who had had special opportunities to study this disease. The South Carolina State Board of Health is to be most heartily congratulated on the success of its meeting, and the publication of this volume.

Light Therapeutics. By J. H. Kellogg, M. D. (*Battle Creek, Mich.: The Good Health Publishing Co., 1910.*)

"As a practical manual for the clinical use of the electric-light bath in its various forms," the object of the author in writing this manual seems to be satisfactorily reached. It is divided into eight chapters on 1, The physics of light; 2, the physiological effects of light; 3, the therapeutics of light; 4, effects of heat and cold and their use in therapeutic combination; 5, technique of light applications; 6, phototherapy plus hydrotherapy; 7, clinical phototherapy; and 8, phototherapeutic appliances. The value of light in its various forms as a therapeutic agent still demands much study, and not all the benefits accorded it by its advocates can be substantiated, but none the less it is useful in certain cases, and this book will help students to learn how it may be best used.

Medical Gynecology. By Samuel Wyllis Bandler, M. D., etc. Second Revised Edition. Illustrated. Price, $5. (*Philadelphia and London: W. B. Saunders Company, 1909.*)

In the preface to the first edition the writer states that the book has been prepared as a result of frequent inquiries for a work dealing with the non-operative side of gynecology. The various topics have been viewed from the standpoints of the symptoms, the disease, the bimanual and microscopic findings, and the general, physical and nervous state. In order to do this repetition and reiteration are necessary but these emphasize the important points and make each section complete in itself, thus diminishing as much as possible the necessity of referring to other sections except for more complete elucidation. He has endeavored to show the relation which pelvic abnormalities really bear to the physical and mental state of the female in order that we may deal intelligently with the gynecologic diseases and not confine our diagnosis and therapeutic methods to the pelvis. The writer states that he has consulted particularly the writings of Kisch (puberty); Joseph (syphilis and gonorrhœa); Bumm, Wertheim and Ringer (gonorrhœa); Oskar Frankl (electricity and hydrotherapy) and especially Winter for much that has appeared in the book.

In the preface to this the second edition he states that the chapters on electricity and hydrotherapy have been enlarged and various other additions have been made to the book as a whole.

The first section is devoted to gynecological examination; the next to a description of the various methods used in the medical treatment of gynecological conditions. This is followed by a very important feature of the book, i. e., the study of the principal symptoms arising from gynecological diseases by stating the causes of each and methods of diagnosis and treatment. The chapters on associated nervous conditions, constipation and gonorrhœa are very thorough and practical. The various gynecological diseases are presented by describing the pathological conditions present, its symptoms, diagnosis, and the treatment indicated.

The work is particularly valuable to the general practitioner because it presents the subject just as it occurs in practice, i. e., from the standpoint of the patient as a whole and not from the consideration of the pelvis alone. J. H. S.

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D. J. H. ... Sarah. 5

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CONTENTS.

IN MEMORIAM.

DR. JOHN HEWETSON.

1867-1910.

The men of the first few years of the existence of this hospital formed a very happy band—young and eager, with a great problem before them, too great, indeed, to be fully appreciated by us. It was a motley group that the gift of a new foundation in medicine had brought together, strangers to each other, strangers in a strange city; yet there was something in the air, and something in the spirit of the place that quickly ripened a mutual trust into good fellowship. The "lead" already given by that great triumvirate, Martin, Remsen and Welch, with Mr. Gilman's strong personality and intense interest in the hospital (which he had opened for the trustees) made the "running" comparatively easy. It has often been remarked that the reputation of the Johns Hopkins Medical School has been made by its young men, to which I may note incidentally my shelves bear weighty testimony in the 12 volumes, with the 500 papers of the graduates of the school during the first 8 years. We were singularly fortunate in the senior assistants with whom the work began, Councilman, Lafleur, Brockway and Robb. I have forgotten how it was that Lafleur came to us from Montreal, probably through my friends Ross and MacDonnell, but it proved a very happy selection, and the "Dane," as we loved to call him, gave a certain *cachet* to the position, which his successors have been keen to appreciate. In the first year we had for house physicians Toulmin from Philadelphia, Reese from Baltimore, and "Al" Scott from Philadelphia, all congenial spirits and enthusiastic workers. Reese was cut off by tuberculosis at the very outset of a brilliant career; while his many friends had to lament Scott's untimely death last year. As the work grew the following year Simon and Hoch came into the house. Then, in the summer of 1891, Thayer joined the staff, and in October succeeded Lafleur as first assistant. In 1890 there came to us, probably through the influence of Lafleur, John Hewetson from McGill, who had just finished a term of residence at the Montreal General Hospital. I have just had the sad news of his death, and wish to pay a brief tribute to his memory. Long practice has given me a fair control of my vaso-motors, but my grip has never been sure when a letter or some incident brought suddenly to my mind the tragedy of the life of "Jack" Hewetson. As I write there comes the far-away vision of a young face, frank and open, with the grey-blue eyes that looked so true, and a voice to match, with a merry laugh—no wonder that everyone loved him! Three happy years he lived with us, growing into a strong, earnest worker, and contributing with Dr. Thayer an important monograph on malaria, and many minor papers. Frank Smith and Barker, who joined the staff about the same time, became his devoted friends. The controller, Mr. Winder Emery, at once fell under his spell, and it was touching to see the affection with which the stern old martinet regarded the younger man. In 1894 Dr. Hewetson went to Germany, and in Leipzig appeared the signs of pulmonary tuberculosis. He had had a pleurisy in Montreal, and the disease made rapid progress. He returned to California, where his father lived, and began to fight the long and losing battle which has just ended. Brave and cheerful, never repining, even in his broken life, much happiness—happiness that comes with a devoted wife and faithful friends. We who loved him in those early days have never recovered from the tragedy of the wreck of a career of such peculiar promise. W. O.

Dr. John Hewetson, the eldest son of the late James Hewetson, of Riverside, California, was born in Bruce County, Ontario, in 1867. He was educated in Canadian schools,

spending several years at Upper Canada College in Toronto. Entering the Medical Department of McGill University, Montreal, in 1887, he was given the degree of M. D., after the regular course of study, by that institution in 1891. During his undergraduate days he was a member of the Zeta Psi Fraternity, and was elected to the highest office in the local chapter.

In 1890 he was appointed assistant resident physician in the Johns Hopkins Hospital, and in 1892 became the first assistant to the resident physician. During his service on Professor Osler's staff, in addition to his routine work, he undertook special studies, including pathological courses in Professor Welch's laboratory, and analyses of the typhoid statistics of the hospital. With Dr. Thayer, who was then resident physician, he made special investigations on malaria; the results were published in the monograph by Thayer and Hewetson entitled "The Malarial Fevers of Baltimore."

The International Medical Congress was held in Rome in 1894; Dr. Hewetson went to Italy to attend the meeting as the delegate of the Johns Hopkins Hospital.

He began his European post-graduate studies in 1894, when he settled in Leipzig and took up work in the Anatomical Institute of Prof. Wilhelm His. After following the course in human embryology he became especially interested in the development of the human nervous system, and under Hans Held prepared several series of exquisite preparations of the medulla, pons and mid-brain of new-born babes, stained after Weigert's method. Stimulated by the lectures of His and Held, and also by the demonstrations of Paul Flechsig, it was his intention to make exact studies of the series he had prepared with the hope of throwing fresh light upon the development of the conduction paths in this portion of the central nervous system. His plans were suddenly interfered with by his discovery of tubercle bacilli in his own sputum in the summer of 1895, while actively engaged in laboratory work. He had suspected the possibility of the disease from some symptoms which had recently developed, especially as he had suffered from an attack of pleurisy in Montreal, and because he knew himself to be predisposed, since his mother and sister had suffered from pulmonary tuberculosis.

Interrupting his work in the anatomical laboratory he set out at once for the hills of Southern Bavaria, where he began his long fight against his malady in Partenkirchen-Garmisch. Later on he spent some time at Les Avants (above Montreux). Subsequently he made a voyage to Australia. In 1897, somewhat improved, he returned to Riverside, California, where he afterward lived, spending the summers in British Columbia, until his death in St. Joseph Hospital, Victoria, B. C., September 22 of this year. His death was doubtless hastened by the loss of his devoted wife in the preceding year.

The preparations on the nervous system which Dr. Hewetson prepared, though they could not be used by himself, were turned over to Professor Mall's laboratory in Baltimore, and served as the basis for a number of studies in that institute. The illustrations of transverse sections and horizontal sections of the medulla, pons and mid-brain in my book on "The Nervous System and its Constituent Neurones" were drawn by Louis Schmidt from these specimens, and the wax model made by Ziegler, of Freiburg, after the reconstruction of Dr. Florence Sabin, also had its origin in Hewetson's sections. A number of under-graduate and graduate students who have worked in the anatomical laboratory in Baltimore on the structure of the nervous system have had the opportunity of studying the original preparations.

Important as the medical work of Dr. Hewetson was, it was over-shadowed by the character and personality of the man, and by his peculiar power of inspiring respect, friendship and affection, as is well shown by the tribute paid to him by Professor Osler in this number of the BULLETIN.

LEWELLYS F. BARKER.

ELECTROCARDIOGRAPHY AND PHONOCARDIOGRAPHY.

A COLLECTIVE REVIEW.

By LEWELLYS F. BARKER, M. D.,

Professor of Medicine, Johns Hopkins University, and Physician-in-Chief, Johns Hopkins Hospital, Baltimore, Md.

The clinical study of diseases of the circulation has, during the past few years, made exceptional advances. In addition to improvements in the time-honored methods of inspection, palpation, percussion and auscultation, a number of new and important modes of investigating cardio-vascular conditions have been introduced, notably (1) the methods of simultaneous graphic registration of apex beat, arterial pulse and venous pulse; (2) the methods, palpatory, oscillatory, auscultatory, of registering maximal and minimal arterial pressures, and (3) the methods of determining the exact size and movements (a) of the several chambers of the heart and (b) of the great vessels by means of roentgen rays (fluoroscopy, roentgenography, orthodiagraphy).

Still more recently another method of investigating the heart, and one based upon an entirely different principle from any of those before mentioned, has been attracting the attention of physiologists and clinicians. I refer to the study of the differences in electric potential which occur in different parts of the heart muscle preceding and during their activity. These differences in electric potential can now, thanks to the invention of extremely delicate instruments for the purpose, be graphically registered as electrocardiograms. The whole

procedure of the study of the electrical changes in the heart is known as *electrocardiography,* and it is the present status of this subject which will be reviewed in this paper. In passing, I may mention, also, the methods of *phonocardiography,* which make an attempt at greater precision in the analysis of the sounds audible over the heart.

Historical Note.

The doctrine of animal electricity has had a chequered career. The fundamental discoveries of Galvani made more than one hundred years ago were at first most enthusiastically received, but they excited temporarily too many hopes which failed of immediate realization and like many other great discoveries Galvani's soon suffered from neglect. Except for the researches of Nobili and later of Matteucci electrophysiology remained almost a sterile field from Galvani's time until about the middle of the last century, when du Bois-Reymond took it up as a special study and revived occupation in it. Though his work and discoveries insured the permaneney of electrophysiological doctrines, interest in the subjest soon became over-extended and suffered an inevitable reaction even during the life-time of the distinguished leader of physiology in Berlin. These experiences of Galvani and of du Bois-Reymond, respectively, have put the medical world on its guard; it is solicitous lest it permit itself a third time to indulge in over-expectation and premature enthusiasm in connection with electrophysiological investigations. In a modest way, however, the studies of the electrical changes which occur in the body are proving to be helpful in the solution of several physiological and clinical problems; perhaps as fruitful and as promising as any are the researches which have been and are now being centered in the electromotive phenomena of the musculature of the heart.

I should like to point out at the very beginning that these electrical studies seem to have to do with the excitation of the heart muscle rather than with its contraction; excitability (or the bathmotropic function in the sense of Engelmann) is a phenomenon analytically separable from contractility (or the inotropic function), and the electromotive changes under consideration appear to be more intimately related to the former than to the latter; indeed we may regard electrocardiography as affording us an entirely novel method of approach to the study of cardiac function since, through it, we seem to have for the first time a *method of measuring and contrasting cardiac excitations.* The *chronotropic* (or timing), the *dromotropic* (or conducting), and the *inotropic* (or contracting) functions were all more or less accessible to investigation before; but now, we appear to have a way of examining also the *bathmotropic* (or excitation) function.

The tissues of the human body present certain electrical phenomena when at rest (so-called *resting current*); but still more interesting are the changes which occur at moments of excitation (origin of so-called *action current*). The principles involved are very clearly explained in Biedermann's *Elektrophysiologie* (1895) and in Samojloff's recent monograph (1909), on both of which I draw freely in the following description. The moment any point of an excitable tissue is stimulated it undergoes an electrical change, becoming electrically negative as regards other points of the excitable tissue not under stimulation. In other words the tissue at the moment of stimulation becomes converted into a galvanic element, the excited point becoming electronegative (or the negative pole of the element) while all the non-stimulated portions of the tissue taken together become electropositive (or the positive pole of the element). A good deal of confusion has arisen regarding the use of the terms electropositive and electronegative. In a galvanic element the zinc is called on the one hand electropositive because in the fluid of the element the current runs down from the zinc to the other metal, but on the other hand, the zinc is at the same time the negative pole of the element since the current through a wire connecting the two metals of the element passes from the other metal to the zinc. All confusion will be avoided if it be kept in mind that the stimulated point in the excitable tissue becomes negative in the sense in which the zinc is the negative pole of a galvanic element. This can be well illustrated by the simple diagram (Fig. 1) used by Samojloff. If in the excitable tissue *AB* the point *a* undergoes excitation

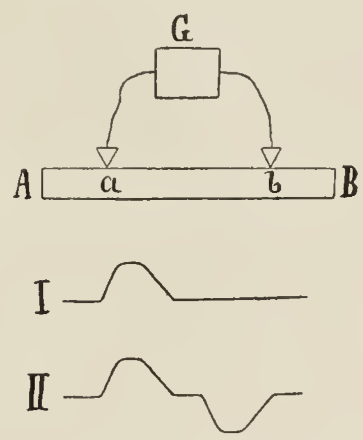


Fig. 1.—Scheme illustrating the action currents in an irritable structure (from Samojloff (A.), Elektrokardiogramme, Jena, 1909).

it will become electronegative in the sense above mentioned, and if two electrodes, connected with a galvanometer *G*, be applied at the points *a* and *b* a current will flow in the excitable tissue from the place of higher potential to that of lower potential, *i. e.,* from *a* to *b,* while in the outer part of the circuit the current will flow from *b* through the galvanometer to *a*. Now if the excitation be limited during the observation to the point *a* and vary only in its strength (starting from nothing, increasing to a maximum and then returning to nothing) an action-current will arise which, when plotted in a curve (with the intensity of the current as ordinates and the times as abscissæ), will take some such form as *I* in the figure. But the process is usually complicated by the fact that besides excitability the structure possesses the power of conductivity, in which event the excitation will gradually spread from *a* to the other points in *AB* and will ultimately reach the point *b*. The curve may then assume one of several different forms; if when *b* is reached *a* is again at rest the action-current would present two phases with opposite signs, say like that in *II* of the figure, which shows a diphasic cur-

rent in which a is first negative as regards b and later b is negative as regards a. Or, the excitation may reach b before a is at rest, and in that event the curve will represent the algebraic sum of the curve for the excitation process at a and the curve for the excitation process at b. The exact form of the curve will depend upon the duration and intensity of the excitations at a and b, on the velocity of conduction through the irritable structure and upon the distance between the electrodes.

We have begun by assuming a knowledge of the course of excitation in the system AB and have constructed a curve which a galvanometer thrown into the outer circuit would yield. By a reversal of the process one sees at once the application of the electrophysiological method. Assume that the excitation-process in the system AB is unknown; by experiment lead off the action-current by electrodes applied at the points a and b; a study of the galvanometric curve obtained will form the material from which inferences may be drawn regarding the excitation in the system AB. Thus if it were possible to lead off the current from the living heart of a man or an animal, the curve of the action-current obtained (or so-called electrocardiogram) would permit us to investigate the happenings in the heart muscle in an entirely new way.

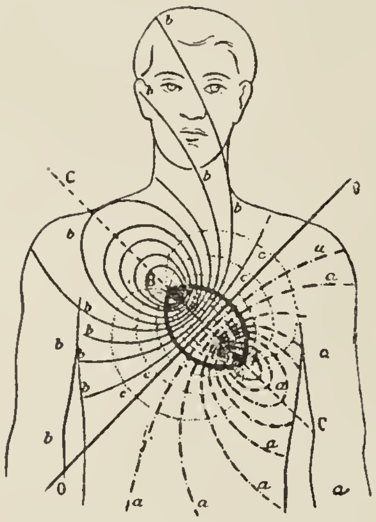


Fig. 2.—Distribution of cardiac electricity on the surface of the body (after Waller (A. D.), Phil. Trans. Roy. Soc., Lond. (B), 1889).

As early as 1865 Koelliker and Müller had demonstrated the rhythmic current variations in the beating frog's heart by means of the rheoscope and had found two elevations in the same direction on the curve during the contraction of the ventricle. A great step forward was made in 1889 when A. D. Waller for the first time demonstrated the possibility of galvanometric registration of the action-currents emanating from the human heart. The idea occurred to him that, though the heart is not directly accessible to the electrodes, still it is practically accessible electrically since it is surrounded on all sides by masses which conduct the electric current. The action-currents in the heart thus affect the potential of the tissues of the whole body and by connecting electrodes with the moist skin it is possible to lead off the currents and to measure their strength by means of a galvanometer. Naturally the form of the curve will vary with the sites of derivation of the current; the curve when the current is led off from the two hands will be different from that led off from the right hand and right foot and both in turn from that led off from the left hand and the left foot. Waller's scheme of the distribution of the potential-differences in the body is shown in Fig. 2. It pictures the body as divided into two parts separated by an oblique plane, the part above and to the right taking on the electrical tension of the base of the heart and the part below and to the left acquiring the electrical tension of the apex of the heart. Though this scheme has had to undergo some modifications as a result of subsequent studies and is limited in that it pays attention to only two points in the heart muscle, one at the base and the other at the apex, still it suffices to illustrate the principle of the derivation of the action currents.

At the time of Waller's work the most sensitive apparatus available for measuring feeble electric currents was the capillary electrometer; a curve was obtained by photographing the movements of a mercury meniscus (Fig 3). The lag or inertia of mercury is, however, so great that the curve obtained had to be corrected by rather elaborate mathematical calculations in order that a true idea of the electrical variation could be gained. While Waller evolved the method of leading off the currents from the living heart and made as good electrocardiograms by photographic methods as could be made with the means at his disposal, he had no idea that any clinical application of electrocardiography would be made.[1]

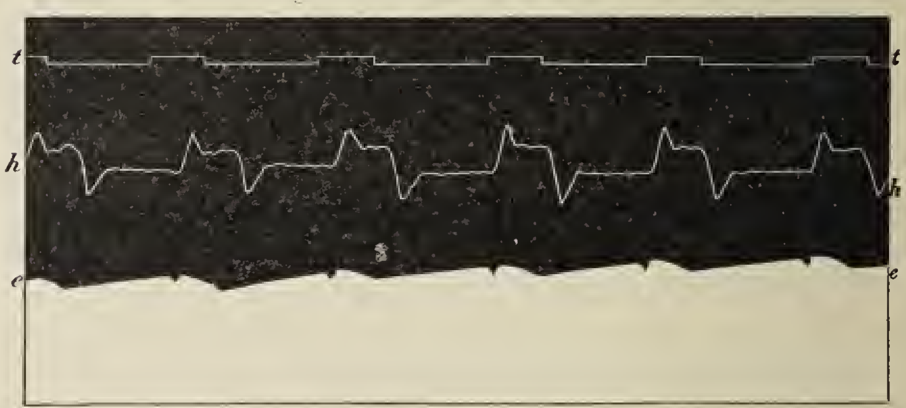


Fig. 3.—The action currents of the human heart (*ee*) recorded by the capillary electrometer registered simultaneously with the cardiogram (*hh*). The time marker gives the tracing *tt* (after A. D. Waller).

[1] Writing even very recently (May, 1909), Waller admits this and, to my surprise, despite his admiration of the delicacy and accuracy of Einthoven's string galvanometer, still fails to see any or only a very slight clinical future for the procedure. He writes as follows:

"I do not, however, imagine, nor, I believe, does Einthoven, that the string galvanometer, however useful and even necessary it may be in the physiological laboratory, is likely to find any very extensive use in the hospital as affording means of physical diagnosis more searching than those in daily use. It can at most be of rare and occasional use to afford a concrete graphic record of some rare anomaly of cardiac action, as it has already in the hands of Einthoven, Lewis and others served to bring into clear evidence the extraordinary disorders of contraction of which the diseased heart is capable. But for all ordinary purposes of diagnosis the finger tips of the physician will hardly

By far the most important step in electrocardiography was made in 1903 when the Dutch physiologist Einthoven of Leyden devised his string galvanometer based upon the suggestions of Ader (Compt. rend. Acad. Par. 1877) regarding an instrument for use in international telegraphy. Einthoven's work resulted in an apparatus of extreme sensitiveness, utterly aperiodic, without lag and easily applicable to clinical and physiological research. In the assembling of the galvanometer and all its accessories the mechanician Edelmann of Munich has performed a useful service (*vide infra*).

Einthoven's String Galvanometer and Edelmann's Electrocardiographic Station.

The string galvanometer of Einthoven is truly an instrument to make one marvel. The device has simplified electrophysiological investigation to an extraordinary degree and has made the taking of electrocardiograms of the human heart, in hospital work at any rate, an easy and practical procedure.

Einthoven's studies with the capillary electrometer of Lippmann soon convinced him that though this instrument is aperiodic (that is, when started into movement by a current shows no oscillations of its own which could deform the curve), it does not possess the necessary quickness of response to a given strength of potential when sufficiently sensitive for very feeble currents or, if sufficiently responsive, becomes insufficiently sensitive. A wholly suitable galvanometer must, besides being entirely aperiodic, be almost without lag or inertia and must be sensitive to electric currents of minimal intensity.

All the desiderata have been realized by Einthoven in the construction of his string galvanometer. In most galvanometers the magnet is the movable part and the current to be measured passes through the stationary coils. In Einthoven's instrument an opposite arrangement has been made; the magnet is stationary and the current passes through a movable thread or string. This movable conductor of the current is extremely attenuated, being a thread of 0.001-0.003 mm. in thickness. Two kinds of threads are used—either one of quartz (coated with silver to make it conduct) or one of platinum. A very good platinum thread is one 85 mm. long with a diameter from two to four microns (*i. e.*, from one-third to one-half the diameter of a red corpuscle), so delicate that it can be seen clearly with the naked eye only when powerfully illuminated against a dark background. Such a thread is too light to be weighed even with extremely sensitive balances, though its weight has been calculated to be about 0.00262 or 0.00685 milligrams (Einthoven). Of course such threads are expensive; clinicians will probably work chiefly with platinum threads as they are quite sufficient for clinical work and are less fragile than the quartz threads; besides they do not lose their conducting power as the quartz thread may do from scaling off of its silver coating.

The ends of the thread are made stationary, so that the thread swings like the string of a musical instrument—hence the designation "string galvanometer." The relations of the string to the pole-shoes of the magnet are illustrated in Fig. 4. Since the magnet must be strong, it is customary to use an electromagnet, though some of the smaller instruments work very well with non-electric magnets. The string is suspended midway between the pole-shoes (*P, P*, in Fig. 4). It is a well-known physical

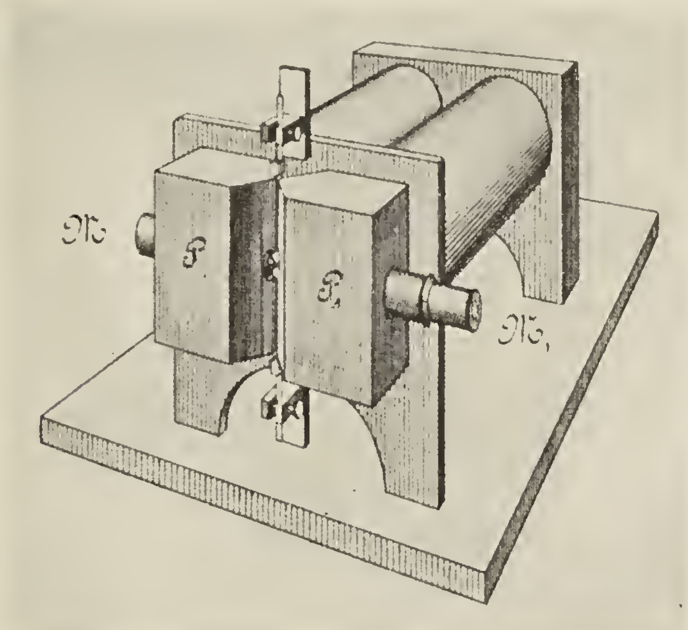


Fig. 4.—The string galvanometer devised by W. Einthoven (from Einthoven (W.), Le Télécardiogramme, Arch. Internat. de Phys., 1906-7, iv, 133).

fact that when an electric current is passed through a magnetic field it undergoes a deflection perpendicular to the lines of magnetic force which pass between the two poles of the magnet; thus when a current passes through the string of Einthoven's galvanometer the current is deflected *and with it the string*. The deflection will be to one or the other side according to the direction in which the current passes through the string; the stronger the current which passes through, the greater the deflection and *vice versa*. The thread of Einthoven's instrument is so delicate that it is suitable only for the measurement of very feeble currents which cause only slight oscillations of the string; a tyro working with the instrument may easily break the thread by permitting too great a deflection from the passage through the string of too strong a current. In order properly to value the oscillations which result from the passage through the galvanometer of the feeble action-currents of the heart a magnifying apparatus is essential. Einthoven perforates the nuclei and poles of the

be helped by an instrument as difficult to manage and to interpret as the string galvanometer."

This judgment has, I fear, been passed without sufficient consideration. Once an electrocardiographic station (of the type devised by Edelmann (*vide infra*) for applying Einthoven's string galvanometer) has been set up, one can more quickly, easily and certainly analyze a cardiac arhythmia by its use than by any other method. The technique, once acquired, is not difficult, and is far less irritating and baffling than that of making phlebograms and arteriograms in difficult cases. It will not, of course, supplant other clinical methods, but that it supplements them definitely and represents a real and permanent advance in the methodology of cardiac investigation no one who has studied any large number both of normal and of pathological cases with its aid can doubt.

magnet in the middle and inserts two microscope-tubes (M and M_1 of Fig. 4) in the openings. One of these is provided with an objective for focussing a strong electric light upon the string; the other is a projection microscopic, consisting of an objective (or of an objective and an ocular) which throws an enlarged image of the illuminated string upon the slit of the photographic apparatus, or upon a white ground on which the movements of the thread may be observed with the naked eye. Thanks to the attenuated nature of Einthoven's string, it is completely aperiodic, the damping by the air together with the electro-magnetic damping (the latter being directly dependent on the field-strength of the electro-magnet) being sufficient completely to prevent any oscillations proper to the string itself; one can be sure, therefore, that the deflection of the thread, on passing a current of definite intensity through, is due to this alone. Again, the fact that the deflections of the thread are really microscopic excursions explains how it is possible to get such an immediate deflection or "setting" of the thread for a current of given strength. Still further, the size of the waves in the curve can be varied not only by the degree of optical magnification of the image of the string, but also, and this is very important, by changing the tension of the string by means of a screw at one end of it; the tighter the string is stretched the smaller the excursions made by the thread and the shorter time it takes for the deflection or setting; and, *vice versa*, if the string be loosened a current of the same intensity will yield a wider excursion but it will be made more slowly. Obviously, therefore, in order that curves of comparable value may be obtained it is desirable to know the sensibility and setting-velocity of the instrument at the times the curves are made. Einthoven recommends for routine examinations of human hearts that the instrument and recording apparatus be adjusted so that in the curve obtained 1 mm. of abscissa corresponds to 0.1 second and 1 mm. ordinate to 10^{-4} volt, or in other words, 1 cm. of excursion of the string in the record represents 1 millivolt. The lag is so slight that the setting requires only 0.001 second. The sensibility with the finest quartz threads is such that 0.1 mm. $= 10^{-12}$ ampere (the photographic record of the excursion being a 1000-fold magnification). It is to be remembered that the thinner and shorter the string, the more sensitive it is (assuming strings of identical quality).

When the string is oscillating to the action-currents of the human heart, only the larger oscillations are discernible to the naked eye even in the magnified projected image. In order to make out the smaller excursions and to obtain curves as permanent records *photographic registration* is essential. Accordingly the magnified image of the string is projected by means of a powerful electric light upon a slit in a dark box which contains a moving photographic film or sensitive bromide paper. The slit opens and shuts when required by electric signal, and the movement of the film can be begun or stopped at will. Ordinarily a film half the length of an ordinary kodak film will suffice for one observation, but when extrasystoles occur but rarely or when for any other purpose observation of all the electrical results of the heart muscle over a considerable length of time is desired, much longer films may be employed. It is best to use a recording apparatus which will permit a photograph 75 meters in length to be taken without intermission. Smaller portions of this long film may be used and clipped off for development as desired.

Since the long axis of the slit in the box is placed horizontally and the string of the galvanometer makes excursions either to the right or to the left, the record on the film which moves vertically in front of the slit is in the form of a curve in which the excursions are up and down; the arrangement is such that when the action-current is due to electronegativity of the base (*i. e.*, is one in which the base of the heart corresponds to the negative pole of a galvanic element), the excursion on the film is in the upward direction, while when the action-current is one indicating that the apex of the heart is electronegative (*i. e.*, the apex corresponds to the negative pole of a galvanic element), the excursion as seen in the film is in the downward direction. When there is no action-

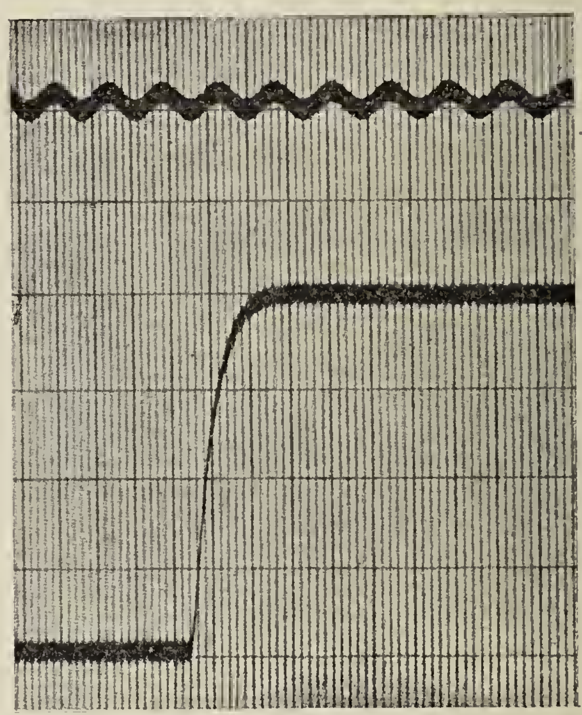


Fig. 5.—Curve showing sensibility of galvanometer. A current of 4 millivolts has produced a deflection which in the record amounts to 4 cm. The tuning-form vibrates 100 times per second (after Samojloff (A.), Elektrokardiogramme, Jena, 1909, p. 9).

current, or when multiple action-currents exactly neutralize one another, the string stands still in its middle position and a straight horizontal line is registered on the recording film.

A lever connected with a chronometer marking fifths or tenths of a second oscillates before one end of the slit, so that exact timing of the excursions in the curve is possible. One can also record on the same film a curve of the carotid pulse by placing before the slit a lever connected with a tambour and receiver; perhaps still better for this purpose is registration of the carotid pulse by means of a telephone and a second smaller galvanometer, the string of which is projected on the same slit. If desired, such a second galvanometer may be used in connection with a microphone, and an electrophonographic record of the heart sounds be made simultaneously with the electrocardiogram upon the film.

Where exact measurements of the ordinates and abscissæ

of the curve are desired the procedure is simplified by the application of a method introduced by Garten; while the photograph is being taken the light is intermittently interrupted by a spoked wheel set up in the path of the light rays; the picture then appears crossed by a series of vertical lines which run parallel to the slit and give a series of ordinates. If in addition a glass slide ruled with parallel lines running perpendicularly to the slit (*i. e.*, parallel to the abscissa of the electrocardiogram to be taken) be placed in front of the latter, the curve will appear plotted upon a network, making exact analyses very easy. In Fig. 5 I have introduced from Samojloff a curve illustrating the effect of the passage of a current of definite strength through the galvanometer arranged in this way. It is easy to see how promptly the excursion of the string from its zero position to its new equilibrium position occurs; one sees no trace of vibrations inherent in the string—the instrument is absolutely aperiodic. The time in this instance is marked by a curve due to a tuning-fork with 100 vibrations per second. Note how brief a time

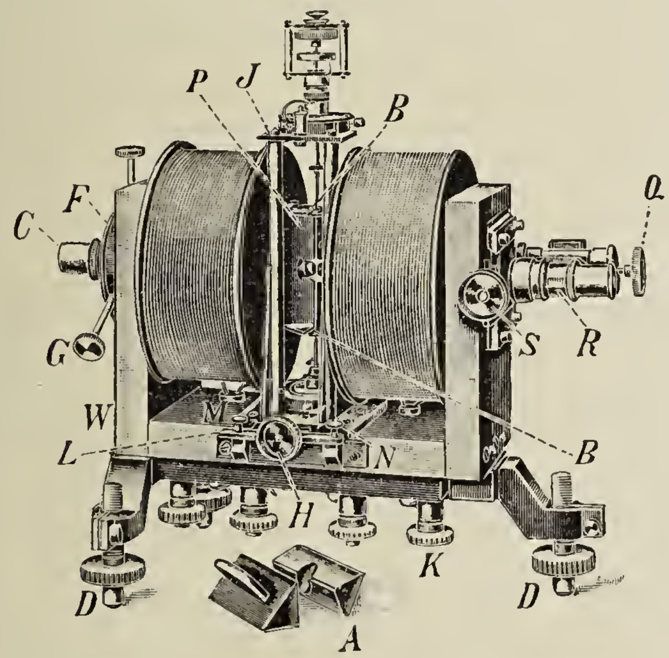


Fig. 6.—String galvanometer (large model) made by the mechanician Edelmann of Munich (from the pamphlet by M. Edelmann, Jr., Munich, 1908, p. 2).

was required for the excursion to become complete (between 0.01 and 0.02 second)—the "setting" was very prompt, showing how little lag or inertia there was to the string. As regards the sensitiveness in this particular instance Samojloff connected the quartz thread (the resistance of which amounted to 6700 ohms) with a portion of a rheochord whose ends showed a difference of potential of 4 millivolts. Since the excursion measures 4 cm. it will be seen that 1 mm. of excursion, in this instance, represents a tension, or electromotive force, of 10^{-4} volt and a current-intensity of 1.5×10^{-8} ampere.

Thanks to the mechanician Edelmann of Munich a complete electrocardiographic station may now be purchased by any hospital and be comparatively easily set up. The electrical "heart-station" consists of (1) the string galvanometer; (2) the electric light for illumination with its accessory apparatus; (3) the electrodes; (4) an apparatus for determining the resistance of the electrodes and of the body; (5) an apparatus for the determination of the sensibility of the galvanometer; (6) an apparatus for the compensation of the "zero current" or body-current, and (7) a photographic registering apparatus.

The electric arc-light should be focussed by means of a condenser, and a water bath is intercalated between the light and the galvanometer in order to absorb the heat rays.

For the details of the string galvanometer the description by M. Edelmann, Jr., in the fifth pamphlet issued by the firm of mechanicians in Munich should be consulted. Suffice it here to say that the original Einthoven construction has been very much simplified. The strength of the magnetic field remains about the same (approximately 20,000 units per cm.). A much shorter thread is used now; whereas the thread formerly employed was 140 mm. long, the Edelmann threads measure 87 mm. in length.

In Fig. 6 a view of the galvanometer is reproduced and in Fig. 7 the portion of it which carries the delicate thread. The thread itself extends between the points *h* and *h*. It can be tightened or loosened by the micrometer screw above.

The thread is accessible from all sides, a fact which makes centering much more easy than with former models.

It is unnecessary to use non-polarizable electrodes. The patient sits in a comfortable arm-chair. Three jars or pans made of zinc and filled with normal salt solution are the simple electrodes

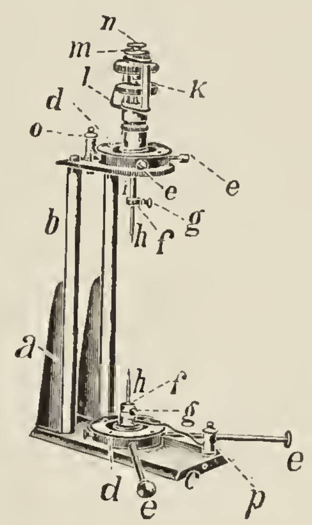


Fig. 7.—The string carrier of the galvanometer (from the pamphlet by M. Edelmann, Jr., of Munich, 1908, p. 3).

employed. These are connected up with wires. The patient places the right arm in one pan, the left arm in another and the left leg in the third. By means of a simple switch any two of these three electrodes may be connected with the galvanometer and one may thus lead off the current by any one of three methods of derivation (D_1, D_2 and D_3, *vide infra*).

Resistance of Body and Electrodes.

The apparatus for the determination of the resistance of the electrodes and of the body of the patient is an application of the principle of the Wheatstone bridge; the adjustment is made with the aid of an induction-coil and a telephone.

By the Wheatstone combination is meant an arrangement of conductors in such a way that a current passes through two branches, between which a transverse connection, the "bridge," exists. In Fig. 8 *E* represents the source of the current (battery); the current between the poles of the battery branches; the four "branches" are designated *a*, *b*, *c* and *d*; the transverse conductor, in which is intercalated a galvanometer *G*, constitutes the "bridge." The direction and intensity of the current which flows through this bridge depend upon the relation of the resistance in *a*, *b*, *c* and *d*. The current in the "bridge" ceases only when

the respective resistances stand to one another in the proportion

1. $R_a : R_b = R_c : R_d$.

Obviously if any three of the resistances are known the fourth one can be calculated; thus—

2. $R_a = R_b \times \frac{R_c}{R_d}$; or, $R_b = R_a \times \frac{R_d}{R_c}$.

For convenience, in place of c and d it is customary to use a so-called "slide-wire," namely a wire of high specific resistance along which a metal contact-clip may be slid. Since in this case c and d are wires of the same quality and diameter it is not necessary to know the values of R_c and R_d in ohms; it is sufficient to know merely the length of c and that of d along with the value of either R_b or R_a in order to determine the fourth resistance at once.

Since in electrocardiography we have to deal with electrolytes, it is desirable to use, not a direct current from a battery and an ordinary galvanometer, but rather the secondary current of a small induction-coil which is generated by an interrupted primary current from a battery. The Wheatstone bridge is thus supplied with an alternating current and the galvanometer is replaced by a delicate telephone. The arrangement is illustrated in Fig. 9.

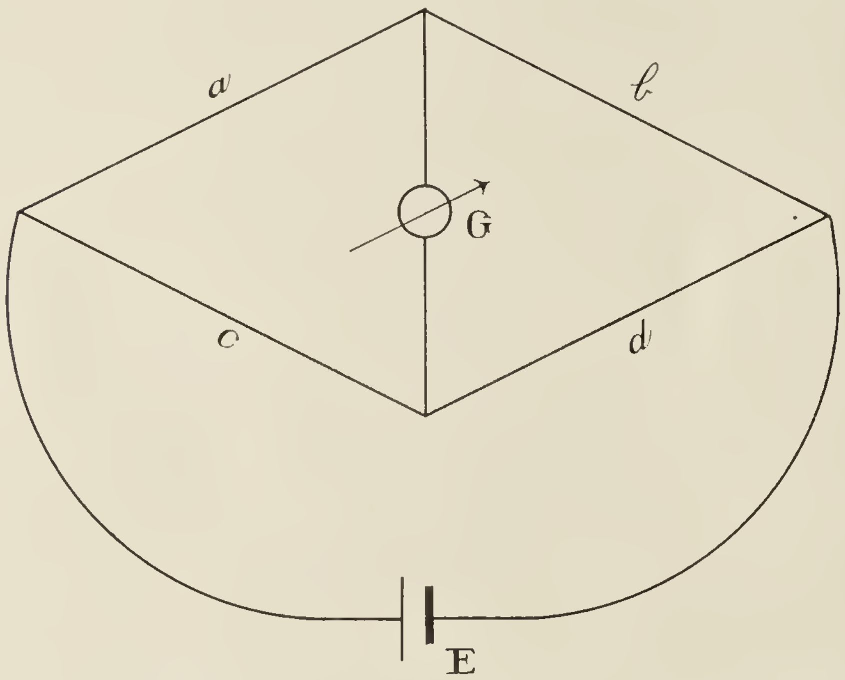


Fig. 8.—Diagram illustrating the principle of the Wheatstone bridge.

Here the source of the current is an induction-coil fed by battery and contact-breaker; the telephone is in the "bridge"; R_b is the resistance offered by the body and the electrodes; R_a is the amount of resistance introduced by an adjustable resistance-varier (rheostat); c is the length of wire to the left of the slide-contact and d the length of the wire to the right of it. Having a resistance of 1, 10 or 100 ohms in R_b, the slide-contact is passed along the wire until a minimal tone is audible in the telephone. Here—

3. Resistance in body and electrodes = Resistance in rheostat $\times \frac{\text{length of } d}{\text{length of } c}$.

The resistance of the body and the electrodes is usually somewhere in the neighborhood of 500 ohms. It is desirable to arrange R_a so that, in extinguishing the current in the bridge, c and d come to be of nearly equal length.

Testing the Sensibility of the Galvanometer.

By the sensibility of a galvanometer is usually understood the strength of current which yields an excursion of one millimeter; thus a galvanometer with a sensibility of 1 milliampere is one in which an excursion of 1 mm. follows upon the passage through it of a current of the strength of 0.001 ampere. When the resistance of the galvanometer is known the so-called volt-sensibility can be calculated from the ampere-sensibility according to Ohm's law:

$$I = \frac{E}{R}.$$

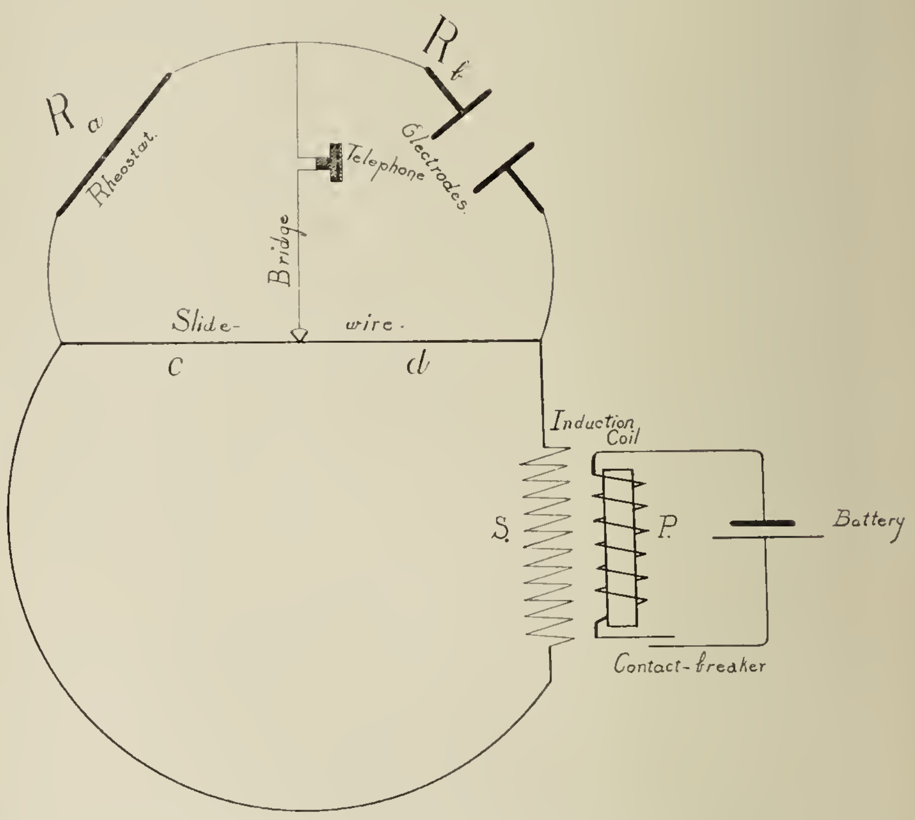


Fig. 9.—Illustration of slide-wire modification of arrangement for Wheatstone bridge.

I represents the intensity of the current in amperes; E the electromotive difference of potential in volts and R the resistance in ohms. Thus, obviously, $E = I \times R$.

If, for example, a galvanometer has the sensibility of 1 mm. =

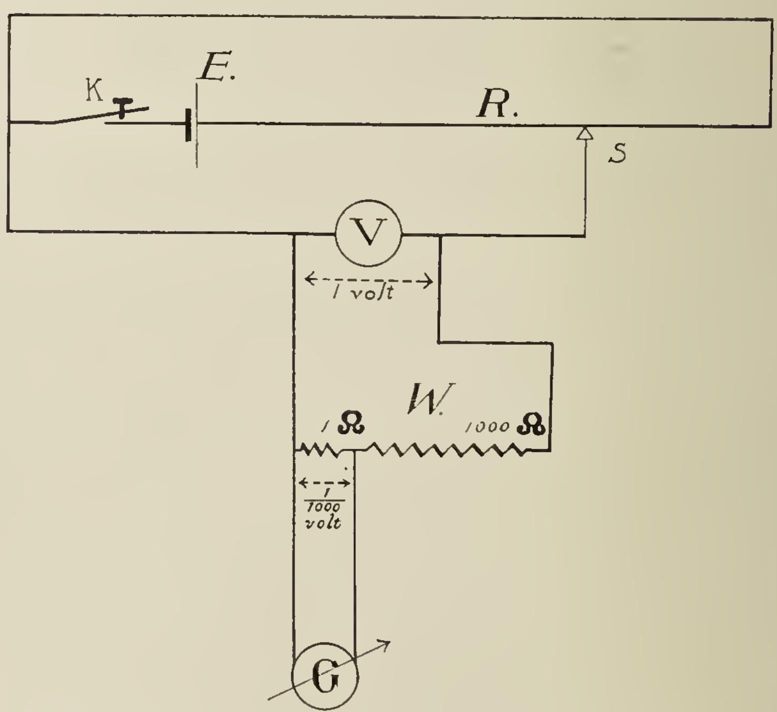


Fig. 10.—Diagram of simple arrangement for securing a current of 1 millivolt.

0.001 ampere and the resistance of the galvanometer is 100 ohms, then the volt-sensibility of the galvanometer is 1 mm. = 0.1 volt:

$$E = I \times R = 0.001 \times 100 = 0.1 \text{ volt}.$$

In the string galvanometer used in taking electrocardiograms it is usual to work with a volt-sensibility of 1 mm. = 10^{-4} = 0.0001 volt; in other words 1 cm. of excursion corresponds to a current of 1 millivolt.

In Edelmann's apparatus the thread is tightened or loosened until the passage of 1 millivolt (exactly measured) through the galvanometer causes an excursion of precisely 10 mm. In order to pass this current through the galvanometer it is desirable to have as a source of the current a so-called "standard cell" or "normal-element," that is, a battery between the poles of which a definite, known and fairly constant difference in potential exists. For this purpose Edelmann uses a Weston Standard Cell.[2]

The electromotive difference in potential yielded is about 1.0192 volts. Of this only 0.001 volt is required. This amount is obtained by arranging for a branching of the circuit and placing parallel to the standard cell a resistance of 101920 ohms; there is then a falling off in potential difference of 0.00001 volt for 1 ohm; if with a rheostat 10 ohms be stoppered off then (practically) 0.0001 volt is obtained. By stoppering off 100 ohms and making the tension of the thread such that an excursion of 10 mm. is obtained the instrument has the sensibility desired.

Since the Cadmium Standard Cell is expensive and unless carefully handled may be easily ruined, we have sought a simpler and less expensive method of sensitizing the galvanometer. At the suggestion of Dr. A. H. Pfund, of the Physics Department of the Johns Hopkins University, we have found an ordinary dry cell (with potential difference exceeding 1 volt), together with an inexpensive volt-meter, entirely satisfactory.

The arrangement of apparatus is shown in the following diagram (Fig. 10) where (E) is a dry cell, (K) a key and (R) a German silver wire. A shunt circuit is connected around the battery and a portion of the wire (R). This circuit contains a pocket voltmeter (V) and a sliding contact (S), the position of the latter being varied until the voltmeter reads exactly 1.0 volt. Next, a resistance box (W) is shunted around the terminals of the voltmeter. The potential difference existing at the terminals of (W) is 1 volt; hence, by stoppering off 1.001 ohms and by shunting the galvanometer (G) around this 1 ohm, a potential difference of 1/1000 (i. e. 1×10^{-3}) volt becomes effective at the terminals of the galvanometer. It only remains to tighten or loosen the thread until, upon depressing the key (K), a deflection of 10 mm. is produced. A deflection of 10 mm. corresponds to a potential difference of 1×10^{-3} volt; hence 1 mm. corresponds to 1×10^{-4} volt, which is the desired sensibility. We can recommend, as sufficiently accurate, this simple procedure, when a standard cell is not available. In Fig. 5 has been shown a curve obtained when a current of 4 millivolts is passed through the galvanometer properly sensitized; the deflection of the string is 4 cm. and the promptness with which the string assumes its new position is obvious when one notes the time-tracing above, where each wave represents 1/100 second.

Compensation of the "Zero-Current."

The body of the patient and the electrodes yield a current which should be neutralized in order that the action-currents from the heart may be studied for themselves. With the aid of an "accumulator cell" (as compensation battery), rheostats, and slide-wire resistance, the compensation is effected so that the galvanometer stands at zero (except, of course, for the excursions due to action-currents). For the details of this procedure the reader is referred to Edelmann's pamphlet.

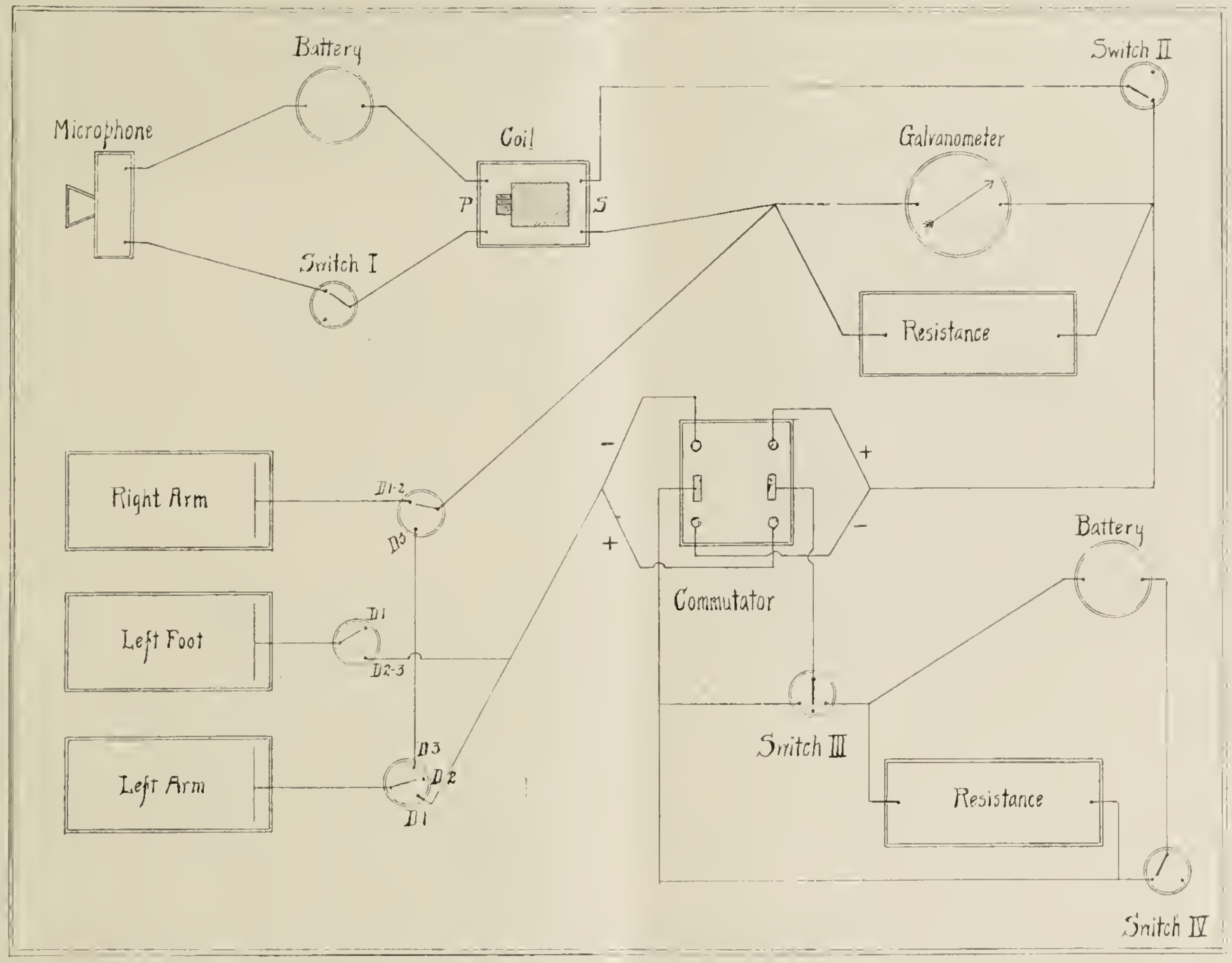


FIG. 11.—The wiring for inexpensive heart station.

Photographic Registration of the Oscillations of the String.

With Edelmann's larger outfit a film 75 meters long is available and as much or as little of it as desired can be used at a single sitting. The film does not have to be changed until the whole 75 meters have been used up; the individual exposures or series of exposures, being numbered, are clipped off as they are made, for development. The film can be passed before the illuminated slit at any one of several different speeds.

Smaller Instruments and Less Expensive Electrocardiographic Stations.

We began our work in electrocardiography in the medical clinic here last year. On account of the cost, it seemed wise to make a

[2] It differs from Latimer Clark's Standard Cell in that cadmium and cadmium sulphate are used instead of zinc and zinc sulphate, and is hence less susceptible to variations in temperature. The amalgam in it contains 10 to 18 gm. Cd. to 90 to 87 gm. Hg.

start with the smaller model of the string galvanometer made by Edelmann (Kleines Permanent-Magnet Saiten-Galvanometer), and to make the wiring so that a microphone could be attached to the same galvanometer for cardio-acoustic work. In the accompanying diagram (Fig. 11), prepared by Dr. Bond, it will be seen how the connections were made.

The patient places left arm, left foot and right arm in the three electrodes represented, which consist of zinc pans filled with normal salt solution (8 grams to liter). From each of these wires are conducted to the three switches, by means of which any two of the electrodes can be connected to the main circuit. This gives the various derivations; D_1 right arm and left arm; D_2 right arm and left foot; D_3 left arm and left foot.

In the wiring of these care should be taken that in arranging for the different derivations, the direction of the current is not changed. The wire from the left foot should always go into the same main wire and in D_3 the left arm electrode should occupy the same position in the circuit as the right arm does in D_2; otherwise an inverted electrocardiogram will be obtained due to this wiring defect.

From these switches the two main wires lead to the galvano-

Fig. 12.—View of inexpensive heart station in the medical clinic at the Johns Hopkins Hospital.

meter, one going directly, the other passing through the commutator. The movements of the commutator do not in any way change the direction of the current generated by the body. The commutator serves the purpose of connecting in and sending in either direction around the main circuit a current from the battery reduced to sufficient strength by the resistance coil. This is sent in the opposite direction to the body current and serves to neutralize the primary body potential ("compensation of the zero-current"). In some instances this factor can be disregarded so that Switch III is for the purpose of completing the main circuit, either including or excluding the battery circuit. A note should be made here that in the latter condition Switch IV should be opened to save the battery from short circuiting through the resistance coil.

On a shunt circuit with the galvanometer is a resistance coil; the greater the resistance the stronger is the current passing through the galvanometer.

The wiring of the microphone is simple. It is connected with a dry battery in a circuit with the primary of an induction coil. Wires from the secondary lead to the junction points of the wires from the galvanometer and resistance coil. The constant battery current passing through the primary induces no current in the secondary. Changes though in the strength of this primary current as the result of sound vibrations on the microphone set up induced currents in the secondary and these are recorded by the galvanometer. Switch I opens and closes the primary circuit, while Switch II serves the same purpose in the secondary.

In Fig. 12 the general appearance of such a small station is shown. In Fig. 13 is another view from behind the small photographic recording apparatus. An enlarged view of the table on which the galvanometer stands is shown in Fig. 14.

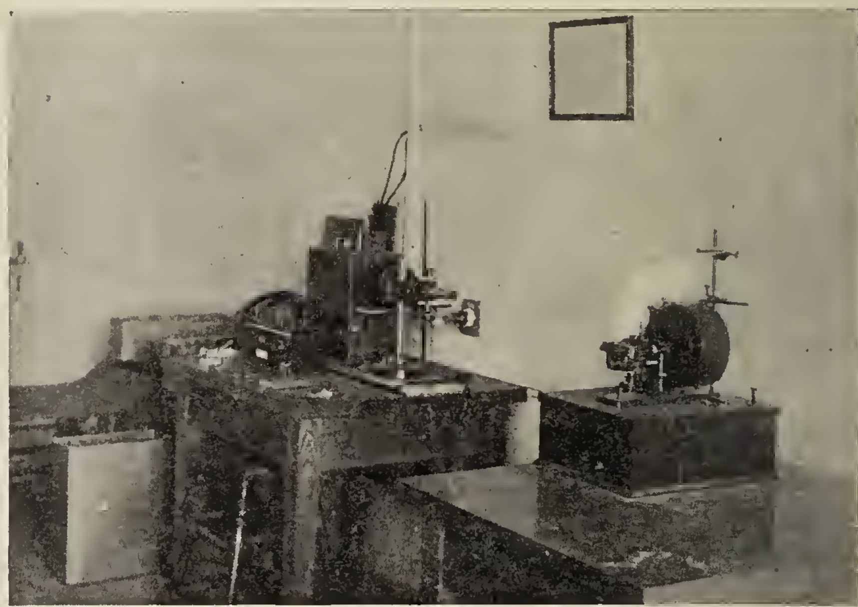


Fig. 13.—Another view of the same heart station.

Tolerably satisfactory electrocardiograms can be obtained with this simple and inexpensive outfit, as will be seen by the records published in the paper read before the Association of American Physicians in Washington, last May,[3] and in the paper by the same authors read before the American Medical Association at St. Louis in June, 1910. For more detailed work, however, the more expensive instrument is desirable. We are now installing

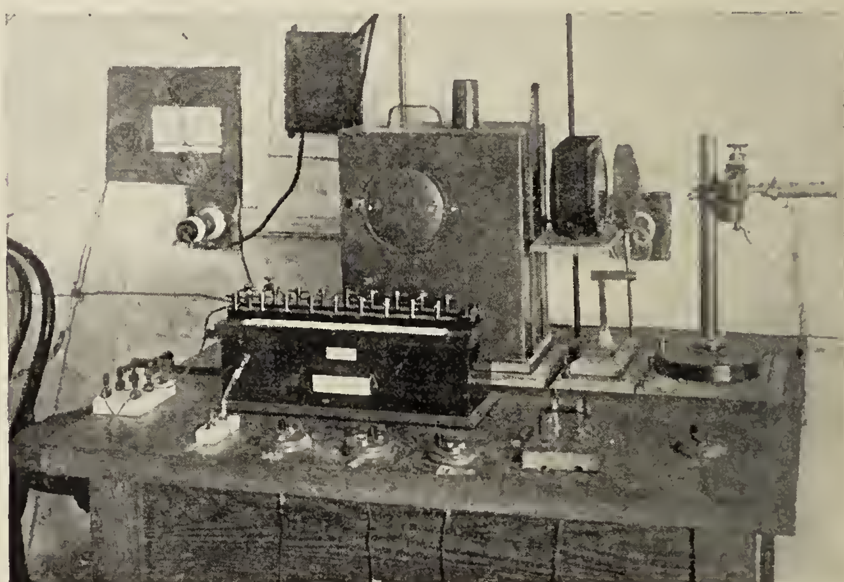


Fig. 14.—Enlarged view of galvanometric table of small station.

a larger and more complete heart station, outfitted with Edelmann's "Grosses Elektromagnet-Saiten-Galvanometer"; this is the one to be recommended for hospital use.

The Typical Electrocardiogram.

In healthy people an electrocardiogram obtained by leading off the current through the two hands under the conditions outlined above assumes, in the majority of instances, the form

[3] Barker (L. F.), Hirschfelder (A. D.), and Bond (G. S.): Personal experience in electrocardiographic work with the use of the Edelmann string galvanometer (smaller model).

shown in Fig. 15. The term "typical" or "schematic" is used instead of "normal," since several slight deviations from the type shown occur in people with normal hearts. The curve for each heart period presents constantly three principal excursions or waves upward (elevations) indicating a negativity of the base of the heart as regards the apex at three different times in a single cardiac revolution. These three elevations have been designated by Einthoven as *P*, *R*, and *T*. The curve presents also, in many instances, two slight excursions or waves downward (depressions), indicating a negativity of the apex of the heart as regards the base at two different times in each cardiac revolution. These two depressions, though less constantly present than the three elevations, have been designated by Einthoven as *Q* and *S*.

The small elevation *P* corresponds in time to the excitation of the two atria, while *R* and *T*, as well as *Q* and *S*, all belong to the time of excitation of the ventricular muscle.[4] The ventricular portion of the curve is conveniently divisible into two parts: (1) that formed by *Q*, *R* and *S*—*R*, by far the greatest of all five excursions, being sometimes designated the *initial ventricular variation;* and (2) that formed by *T* (which

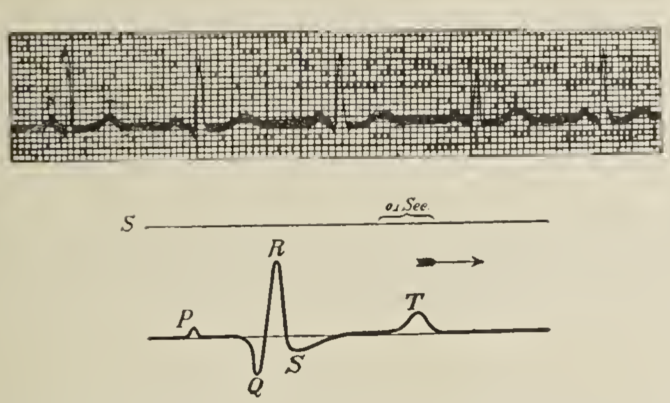


Fig. 15.—Normal electrocardiogram obtained by photographing the movements of a sensitive galvanometer. The upper figure shows the photographed curve, while the lower one is a diagram constructed from the photograph to make clearer the electrical changes in a single cardiac cycle. To obtain this record the electrodes were connected with the right and left hands. Waves with the apex upward indicate that the base of the heart (or the right ventricle) is negative to the apex (or left ventricle). Waves with the apex downward have the opposite significance. Wave *P* is due to the contraction of atrium. Waves *Q*, *R*, *S* and *T* occur during the systole of the ventricle. The curve seems to show that the contraction in the ventricles begins first toward the apex (or in the left ventricle), since the negativity first appears toward that side (wave *Q*). (Einthoven.)

is higher than *P* but lower and slower than *R*)—sometimes called the *after-variation* or *final variation of the ventricle.* The distance between *P* and *Q* (or *R*) represents the time required for the spread of the excitation from the atria to the ventricles and therefore is a good measure of the "$A_s - V_s$ interval" of excitation.

A different terminology for the various excursions or waves of the curve has been suggested by Nicolai (Fig. 16). He pays especial attention to the three elevations which Einthoven calls *P*, *R* and *T*, but prefers to designate them *A*, *I* and *F*, since *A* is the expression of atrial excitation, and *I* and *F* the *initial* and *final* ventricular oscillations respectively. To the less constant *Q* and *S* he applies the terms *Ia* and *Ip* (anterior or posterior to the initial variation), and to similar slight depressions occasionally met with before and after *T* he gives the labels *Fa* and *Fp*. When *R* is doubled, a rare occurrence, he makes the second excursion I_2. The horizontal stretch between *P* and *R* he designates *h* to indicate that the excitation is at that time passing over the His bundle. The stretch from *R* to *T* he calls *t* for reasons to be mentioned later, while the stretch between *T* and the *R* of the next cardiac revolution is labelled *p* to indicate the pause in the heart's activities. I am sorry that this change in terminology has been suggested, especially as some of the ideas upon which Nicolai's lettering are based are still in dispute. It seems to me better not only on account of their priority but also on account of their freedom from explanatory significance to retain the letters used by Einthoven as termini. It cannot help but be confusing if some workers describe their curves in Nicolai's terminology, extremely interesting and important as his work is, while others use Einthoven's. For the present

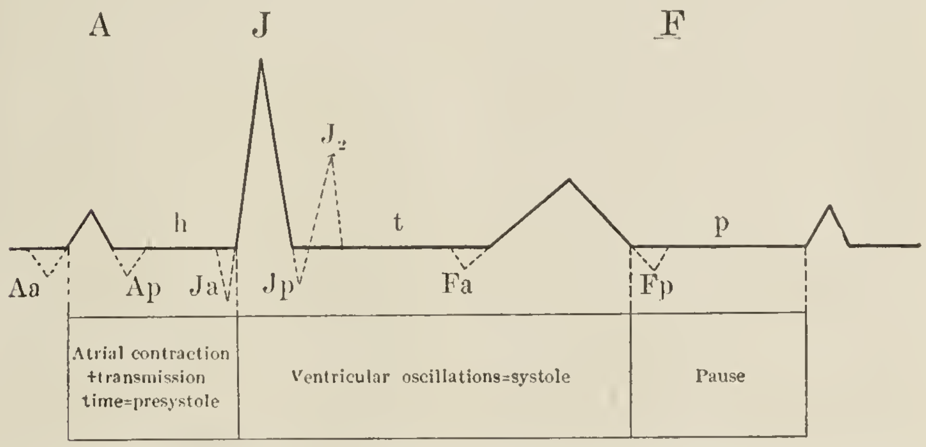


Fig. 16.—Analysis of electrocardiogram according to Nicolai (from Nicolai's article in Nagel's Handb. der Phys. des Menschen, 1909, I, 825).

at any rate I hope that workers in this country will follow Einthoven's lettering of the curves.

The Effect on the Electrocardiogram of Altering the Sites Whence the Currents Are Led Off. Various Leads or Methods of Derivation.

The typical curve shown above was obtained by leading off the current from the two hands. It is not a matter of indifference what parts of the body are chosen for the derivation of the current; indeed there are very characteristic features of the curves from any given individual for different derivation-sites. The following three principal derivation-sites have been used and recommended by Einthoven and may be regarded as standard methods of derivation in making curves from the human heart:

Lead or Derivation I, right upper extremity and left upper extremity (Fig. 17).

Lead or Derivation II, right upper extremity and left lower extremity.

Lead or Derivation III, left upper extremity and left lower extremity (Fig. 18).

---

[4] Hoffmann calls attention to the resemblance of the ventricular portion of the electrocardiogram to the negative variations obtained by Judin from gastrocnemius of the frog.

The different curves obtained by varying the derivation make it imperative that in published curves explicit statements be made as to the methods of derivation resorted to in their production. Moreover, experience has already demonstrated the desirability of systematically making three electrocardiograms from each individual studied, one by each of the three modes of derivation mentioned. Important information may sometimes be gained from one of these which is wholly lacking in the others. I realize that this complicates the procedure somewhat for clinical use, but the advantages are so great that I cannot understand the indifference of Nicolai and Simons regarding the matter, still less the outspoken opposition of Strubell to the use of any derivation-site other than D_1. Strubell's argument is that physicians will be so confused by the use of three different sets of curves from the three derivation-sites that they will be disinclined to consider electrocardiography at all. It seems to me that any physician who will take the trouble to understand the mechan-

Fig. 17.

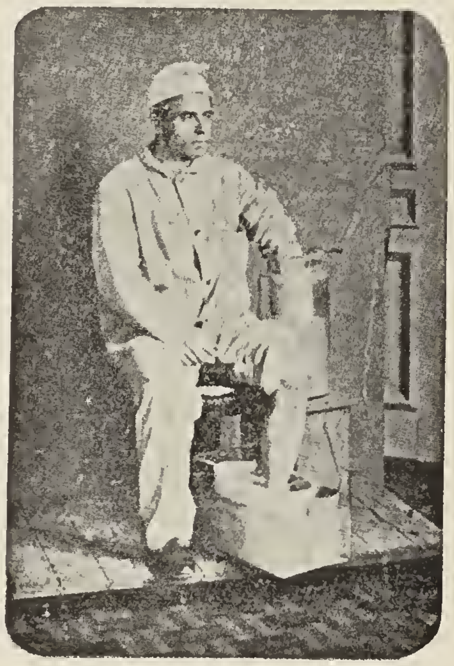


Fig. 18.

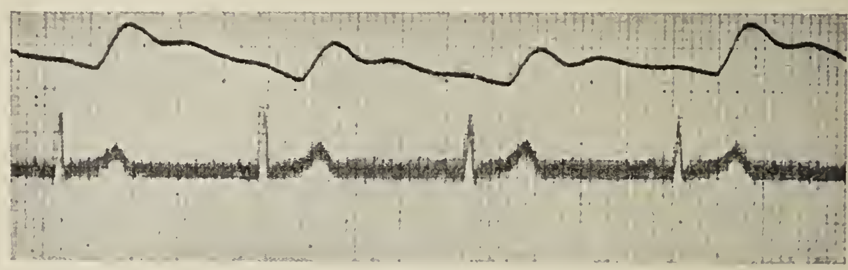
Fig. 17.—Leading off current from the two arms, Derivation I (after Einthoven (W.), Le Télécardiogramme, Arch. Internat. de Phys., 1906-7, IV, 144, Fig. 14).

Fig. 18.—Leading off the current from the left arm and the left leg, Derivation III (after Einthoven (W.), Le Télécardiogramme, Arch. Internat. de Phys., 1906-7, IV, 144, Fig. 15). *a*, Carotid pulse and electrocardiogram, D_1; *b*, Carotid pulse and electrocardiogram, D_2; *c*, Carotid pulse and electrocardiogram, D_3.

ism of the string galvanometer at all and give the matter study enough to make himself familiar with an electrogram taken by D_1 will scarcely turn back if he is told that very distinct advantages are to be gained by the consideration also of the forms of electrograms obtainable by D_2 and D_3. Samojloff puts it well when he says, "One must test the heart for its electrical expression by examining it at different points. Just as one looks at an object from all sides in order better to understand its form, so one must try to ascertain the distribution of electric potential in the heart by successively altering the sites whence we derive the action-current."

In Fig. 19 are given three electrocardiograms taken by Einthoven from one and the same individual, with use of the three chief methods of leading off the current. It will be observed that the three main elevations *P, R* and *T* are recognizable in all the curves but that the appearance of these waves, their height and direction are somewhat different. A further feature, probably very important, is the discrepancy in the times at which the various waves occur with the three methods of derivation; the waves in the curves do not occur in identical phases of the cardiac revolution; that the dimensions of the three curves are definitely related to one another, however, is shown by the fact that the curve obtained by D_2

a



b

c

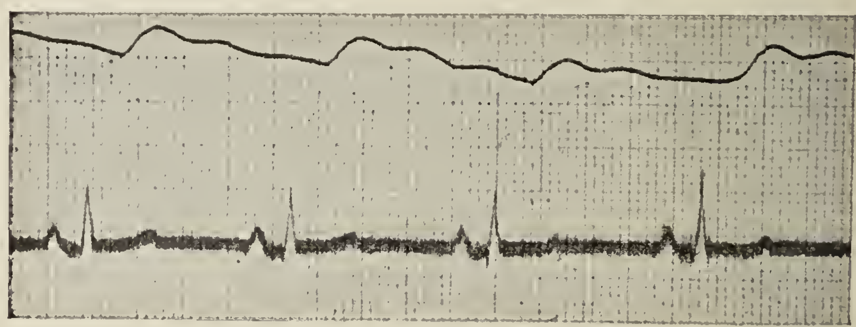


Fig. 19.—Comparison of the forms of electrocardiographic curves obtained by the three different methods of derivation taken from the patient *Ei* (after Einthoven (W.), Weiteres über das Elektrokardiogramm, Pflüger's Arch., 1908, CXXII, 554, Figs. 16, 17, 18).

is approximately the algebraic sum of the curves obtained by D_1 and D_3. This may be expressed as the formula,

$$D_2 = D_1 + D_3.$$

If one examines a series of such curves he will be struck by the fact that this rule holds fairly well for the individual waves; thus for the wave *R*—

$$R_3 = R_2 - R_1,$$

and since T_1 is often as large or larger than T_2, we find that T_3 may be absent or even a depression instead of an elevation. In a rough way, therefore, given the curves by two of these methods of derivation, the third can be reconstructed from them. Not that such reconstructions are especially neces-

sary as a control of accuracy of the recording method, for the method of registration is now more accurate than any third curve reconstruction from the other two could be.

Hoffmann has recommended two other derivations for human beings. In one of these, which he calls derivation IV, he leads off the currents from the right arm and from the left parasternal line three fingers' breadth above the rib margins. In the other, which he designates derivation V, the currents are led off from the right arm and from the angle of the scapula in the back. It seems scarcely probable that derivations other than I, II and III will be necessary for routine clinical work.

The exact form of the curve in each of the several derivations depends largely upon the position of the heart. Waves which are small or absent in a curve obtained by one derivation may be well marked in a curve obtained by another derivation. In contrast with the asynchronism of the waves of typical electrocardiograms in the three derivations is the synchronism of the waves of the atypical electrocardiograms yielded by all three derivations in ventricular extrasystoles (*vide infra*). Observations on human beings and on dogs show that, as a rule, curves taken by derivation II yield the highest waves. A striking feature of the curves taken from patients with hypertrophy of the right or left ventricle is the large potential differences revealed by D_3.

Combined Electrocardiograms and the Comparison of the Electrocardiograms of Two Individuals with One Another.

As has been pointed out above, there may be slight deviations in health from the "typical" or "schematic" electrocardiogram described. The curve yielded by a single individual is, however, peculiarly constant if taken always under the same conditions. Electrocardiograms recorded over a period of one and a half years in the same individual have proven to be very similar to one another (Samojloff). As far as the instrumental side of the record is concerned, it is easier to realize identical conditions of registrations with the string galvanometer than with a sphygmograph.

In order to compare the curve yielded by two individuals at the same moment and with the same apparatus, various observers (Waller, Samojloff) have led off the currents from two people at once (*combined electrocardiograms*). This can be done in two ways, either by having one person with his right hand grasp the left hand of the second individual, the other two hands being immersed in the fluid of the electrodes, the two individuals facing the same way; or by having the two persons stand opposite one another, each facing in a different direction, their two right hands being placed in the fluid of the one electrode and their two left hands in the fluid of the other electrode. To use terms employed in describing the union of electric batteries the former arrangement may be called the *series method* and the latter arrangement the *parallel method.*

In Fig. 20 I have reproduced a curve taken by the series method by Samojloff and in Fig. 21 one taken by the parallel method by the same observer. It will be noted that the waves from the two hearts by the first method have the same direction, while in the second method they have an opposite direction on the film. In the portions of the records shown the waves due to the two hearts are easily recognizable. In the long original curves there are parts where the waves overlap or interfere with one another in such a way as to make recognition of the individual electrocardiograms difficult or impossible. Those who have taken combined electrocardiograms point out that the principal difference in the curves compared

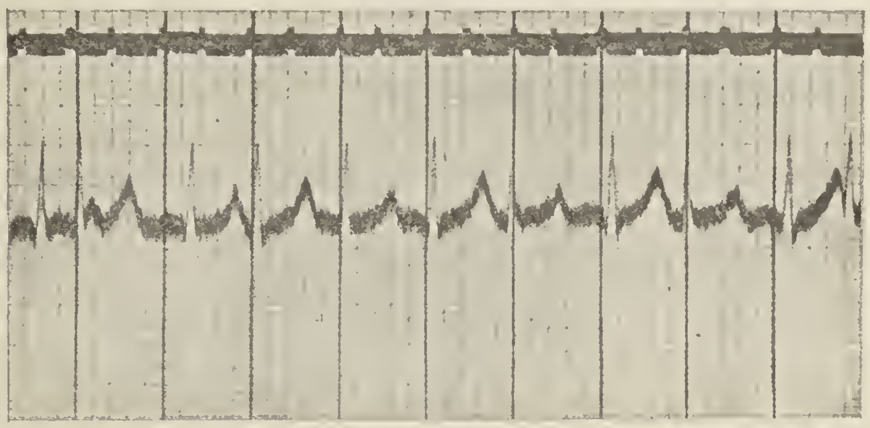


Fig. 20.—Combined electrocardiogram of two human hearts; arrangement in series. 1 cm. ordinate corresponds to 1 millivolt. Time markings 0.25 sec. Magnification 460 (after Samojloff (A.), Elektrokardiogramme, Jena, 1909, p. 26, Fig. 13).

lies in the height of the wave T, whereas the waves P and R are more nearly equal. It is interesting that the curves permit not only the decision that two hearts are beating but also a conclusion regarding the reciprocal orientation of the individuals under observation.

An ingenious application of the combined electrocardiogram has been made by Cremer of Munich. This physiologist recorded the curve (by a special method of derivation) from

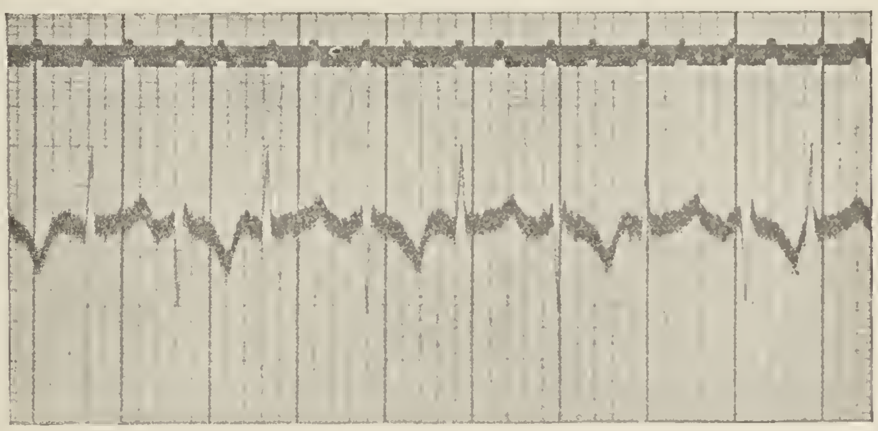


Fig. 21.—Combined electrocardiogram of two human hearts; arrangement in parallel. 1 millivolt corresponds to 1 cm. ordinate. Time marker 0.25 sec. Magnification 460 (after Samojloff (A.), Elektrokardiogramme, Jena, 1909, p. 27, Fig. 14).

a pregnant woman and was able to distinguish the waves due to the fœtal heart from those due to the mother's heart (Fig. 22). The possibility of confirming clinical obstetrical diagnoses and even of making positive diagnoses in otherwise doubtful cases by the aid of the string galvanometer is obvious. It seems probable that twin and multiple pregnancies may be easily diagnosed in this way; further, it is believed that with the aid of several derivations it may be possible to come to a

decision as to the reciprocal positions of the twins in the mother's body.

An effort has been made to regard the typical electrocardiogram taken from a healthy person as the combined electrocardiogram of the right and left sides of the heart. Kraus and Nicolai have gone farthest in this direction and base their opinions chiefly upon curves obtained when there is a lack of synchronism between the activities of the right side and the left side of the heart. Whether their conception is a correct one or not, further experience must determine. The relation to the clinical conception of hemisystole is obvious and Kraus and Nicolai maintain that such a clinical hemisystole is a reality.

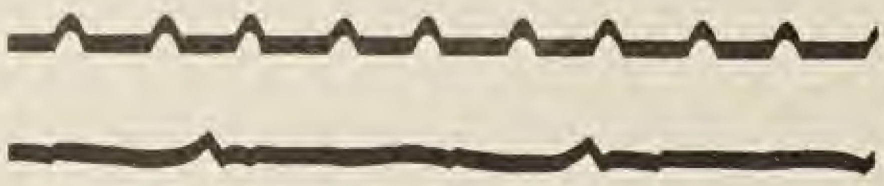


Fig. 22.—Electrocardiographic curve taken from pregnant woman, showing beats both of maternal and of fœtal heart (after Cremer (M.), Münch. med. Wchnschr., 1906, I, 813, Fig. 24).

The Telecardiogram.

For several reasons it is often desirable to take tracings from patients who may be a considerable distance from the electrocardiographic station. In the first place many cardiac patients are too ill to be removed from a hospital ward to the heart station. Again in many instances an electrocardiographic apparatus will be set up in a physiological laboratory when one is not available in a hospital in the same town. To meet these requirements wires may be laid connecting various wards of the hospital with the heart station which is situated either in the hospital itself or in a physiological laboratory in the same town. Einthoven in Leyden laid wires between the Leyden Hospital and his laboratory, a distance of more than a mile, and took tracings in his laboratory from patients in the hospital wards. The main difficulty lies in the prevention of induced currents en route, but that such *telecardiograms* are feasible has been fully demonstrated.

A Comparison of the Electrocardiogram of Certain Animals with that Obtained from Man.

Physiologists naturally worked largely with animals, though the early studies were made with the aid of the capillary electrometer. For the more important observations we have to thank Waller, Gotch, Gaskell, Einthoven and Buchanan.

In recording electrocardiograms from animals, certain special methods have to be employed. The animal must be kept quiet, and for this purpose anæsthesia may be necessary. Electrodes of special type are used and one of the best methods of derivation is to lead the currents off from the œsophagus and from the anus. The sensitivity and speed of setting of the galvanometer have to be adapted to the particular animal under observation.

In Fig. 23 is reproduced the electrocardiogram taken from a dog; good curves from the frog are given in Samojloff's article in Engelmann's *Archiv*, 1906, *Suppl. Bd.* It is a very remarkable fact and very important for our understanding of the animal electrocardiogram that the frog's heart, which has only one ventricle, yields practically the same form of electrocardiogram as that given by a mammal. The similarity of the electrocardiogram yielded by the dog to that given by man is still more striking. These facts are of great importance for experimental physiology, for obviously, since the electrocardiograms of healthy animals are very similar to those of normal man, experimental modification of the electrocardiogram in dogs may be undertaken confidently, with the expectation that they will throw light upon pathological curves in human beings (*vide infra*).

One interesting application of the electrocardiogram has been the determination of the frequency of the heart beat and the form of the electrocardiogram in birds. Buchanan[5] has ascertained the frequency of the heart beat in a gold-finch, two green-finches, four sparrows, three pigeons and three hens. James Mackenzie had previously ascertained the frequency in a hen to be about 270 per minute. It turns out that the gold-finch's heart beats between 900 and 925 times per minute, the green-finch's heart between 700 and 848 times per minute, the sparrow's heart between 745 and 850 times per minute, the pigeon's heart between 141 and 225 times per minute, the hen's heart between 304 and 345 times per minute.

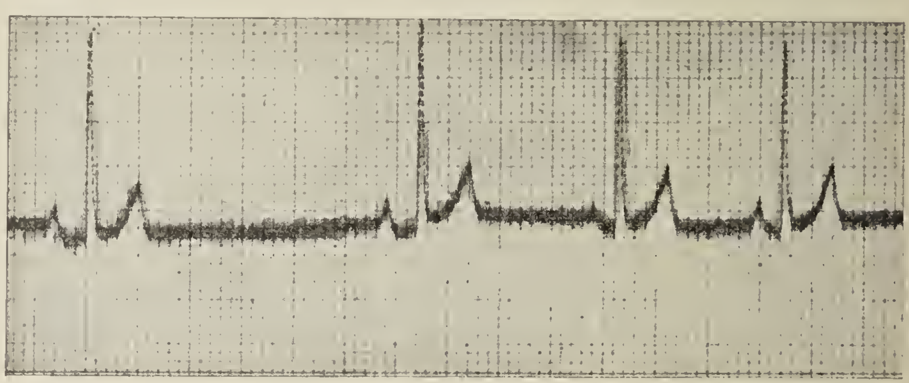


Fig. 23.—Electrocardiogram of dog's heart; D_2. Abscissa 1 mm. = 0.04 sec.; ordinate 1 mm. = 10^{-4} volt (after Einthoven (W.), Weiteres über das Elektrokardiogram, Pflüger's Arch., 1908, CXXII, 528, Fig. 3).

On Certain External Influences which may Modify the Form of the Electrograms.

In a preceding paragraph the modifications of the electrocardiogram dependent upon the mode of derivation of the currents were referred to. It is necessary to understand also the effect of certain extra-cardial influences which may have an effect upon the form of the curve in order that modifications due to these shall not be regarded as evidences of change in the heart muscle.

Aside from the sensibility and setting of the galvanometer, polarization of the electrodes, shaking of the galvanometer, the following are the principal points to be attended to. The patient should sit in a comfortable chair with all his

[5] Buchanan (F.), The frequency of the heart beat and the form of the electrocardiogram in birds. J. of Physiol., Camb., XXXVIII, 1909, 62-66.

muscles relaxed since muscular tensions and contractions may modify the curve. Einthoven insists upon the patient sitting in a room separate from that in which the galvanometer is located, the two rooms being connected by wires. In hospitals the various wards may be connected by wiring with the heart stations. In Einthoven's laboratory in Leyden, the galvanometer records the currents of hearts of patients in the hospital a mile and a half away (*telecardiograms*).

The patient should breathe quietly. Respiration appears to affect the curve sometimes and not at other times. According to Einthoven the system of waves Q, R and S is depressed in deep inspiration. Sometimes only the wave R is diminished. These changes do not appear to be due to contraction of the respiratory muscles themselves, nor does the change in the position of the heart through the fall of the diaphragm or the expansion of the thorax seem sufficient to explain the effect since only Q, R and S are affected while P and T are not. Nor would it seem probable that a modified contraction due to the action of the vagi or the accelerator nerves is responsible, for the changes occur without phase change precisely at the moment of deepest inspiration, and this would hint at some mechanical connection between the breathing movements and the electrical effects rather than a circuitous effect by way of the central nervous system. This idea is supported by Einthoven's observations—and it is to Einthoven especially that we are indebted for our knowledge concerning respiratory influences upon the electrocardiographic curve—of dyspnœa and Cheyne-Stokes breathing. In Fig. 24 I have reproduced his curve taken during violent dyspnœa; the other curve taken during apnœa can, he asserts, be scarcely distinguished from this one. They are so nearly identical that one can probably exclude the effect of the dyspnœa itself. Einthoven believes that the respiratory influences he has noted depend upon negative interpleural pressure, which is stronger on inspiration and could exert a definite influence upon the circulation. This influence would affect the right heart more than the left and this he thinks is the reason why the Q, R, S system is more modified than T.

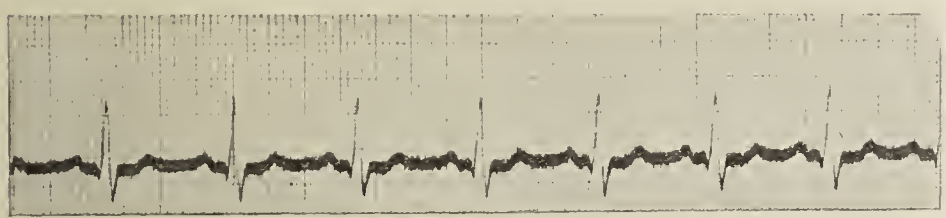


FIG. 24.—Electrocardiogram taken from a patient with Cheyne-Stokes breathing during a period of marked dyspnœa; D_1 (after Einthoven (W.), Weiteres über das Elektrokardiogramm, Pflüger's Arch., 1908, CXXII, Taf. XII, Fig. 8. Only a portion of the original figure is reproduced).

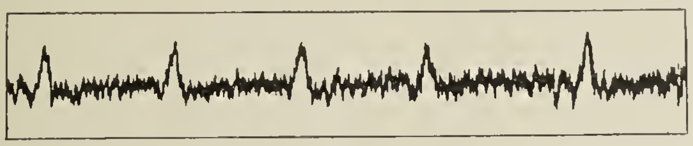


FIG. 25.—So-called splintering of the curve in myocardial disease (after Kraus and Nicolai).

Tremor of the hands of a patient will modify the curve and will sometimes give it a splintered appearance. It is not unlikely that the splintering of the curve described by Kraus and Nicolai (Fig. 25) in myocardial disease was due to tremor of the hands of the patient. The "splintering" is rather too fine to be accounted for by atrial fibrillation. Strubell has shown the effects of tremor on the curve in the hands of masseurs, gardeners and others. In old people and in weak individuals the effects of tremor should be noted. In the curves which we have taken in the Johns Hopkins Hospital from patients suffering from exophthalmic goitre the fine tremor does not seem to have caused much deformity of the curve. It would be interesting to take up systematically the study of different tremors (Graves's disease, Parkinson's disease, etc.).

A remarkable deformity of the curve is that which is produced by induction from alternating electric currents in the neighborhood of the instrument. The galvanometer is extremely sensitive to induction effects, especially those coming from the alternating current. Rothberger has pointed out that many of the curves published by Kahn (Pflüger's Arch., Bd. 126) show exactly one hundred oscillations per second.

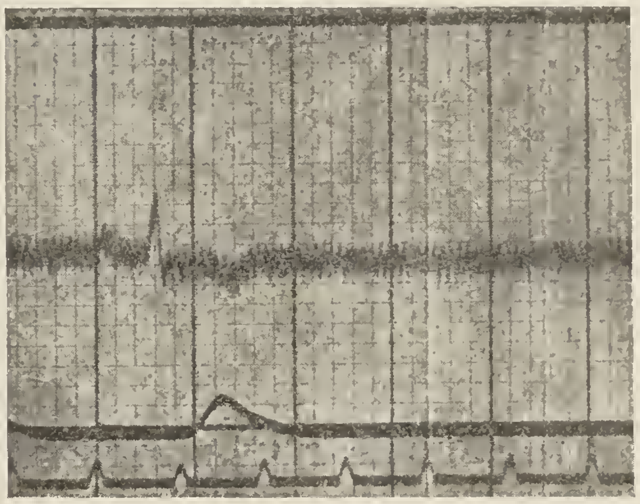


FIG. 26.—Regular tremor of the string due in all probability to induction from alternating current (after Kahn (R. H.), Pflüger's Arch., 1909, CXXVI, Taf. IX, Fig. 7. Only a part of the original figure is reproduced).

Kahn thought that these were due to jars of the instrument, but it seems likely that they were induction effects from an alternating current (Fig. 26).

Another very interesting factor which influences the form of the curve is the position of the heart itself in the thorax. This has been studied by Hoffmann and by Einthoven. Hoffmann showed that displacement of the apex of the cat's heart to the right distinctly affected the form of the curve and he has made observations on human hearts dislocated by pleural effusion and by blowing up the stomach. Strubell suggests that observations be made on patients when the stomach is empty on account of the influence of displacement.

Einthoven and Lint believe that the exact position of the heart in the thorax can often be determined by electrocardiographic examination with the three methods of derivation. They maintain that the height of the waves alone will show whether the heart axis is directed more from behind forward in one individual than in another.

A careful study of the relation of the electrocardiogram to the configuration of the thorax and the position of the heart (with orthodiagraphic control) has recently been made by H. Grau.

Clinical Observations in Human Beings.

Though the method is very new, it has already been introduced into the clinic by Einthoven, Kraus and Nicolai, Strubell, Hering and Kahn, Rothberger, Hoffmann, Lewis and others. In this country electrocardiographic outfits are being set up in the clinics of several of our larger cities. We have mentioned the heart-station at the Johns Hopkins Hospital; an excellent installation of the largest model and of the best photographic registration-apparatus has been made by Dr. Walter James at the Presbyterian Hospital in New York. He was able to demonstrate excellent curves at the association of American Physicians in Washington last May. In this article I shall refer almost entirely to European observers, reserving most of the curves made in our own clinic in Baltimore during this past year for the articles to be published in collaboration with Dr. Hirschfelder and Dr. Bond.

Among other clinical conditions which have been investigated may be mentioned: (1) the hypertrophy of the atria in mitral stenosis; (2) hypertrophy of the right ventricle in mitral stenosis; (3) hypertrophy of the left ventricle, especially in aortic insufficiency; (4) ventricular extrasystoles; (5) the tachycardia of exophthalmic goitre; (6) heart-block cases; (7) congenital heart disease; (8) atrial paralysis and pulsus irregularis perpetuus with atrial fibrillation; (9) the hearts of neurasthenic patients; (10) the hearts of infants; (11) paroxysmal tachycardias; (12) gallop-rhythms.

HYPERTROPHY OF THE ATRIA IN MITRAL STENOSIS.

The atria (or auricles) are the chambers of the heart least accessible to physical examination. Our knowledge hitherto regarding the activity of the right atrium has depended chiefly

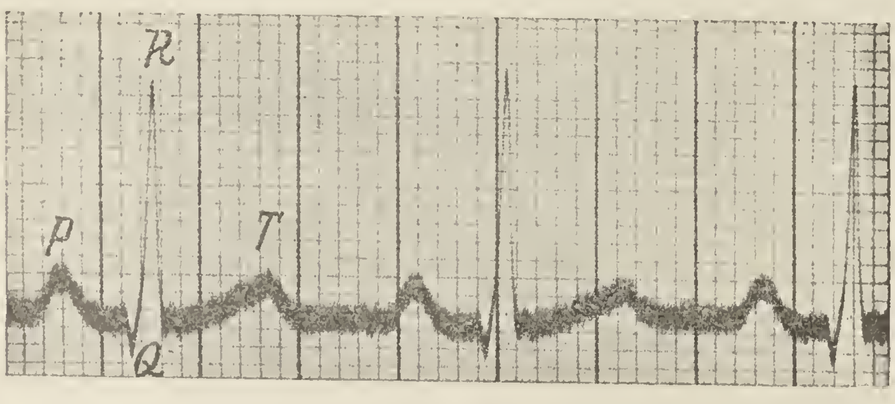


Fig. 27.—Electrocardiogram from a case of mitral stenosis. Note the exaggeration of the P-wave. I millivolt $=$ 1 cm. ordinate, while 1 cm. of abscissa $=$ 0.2 sec.; D_2 (after Samojloff (A.), Elektrokardiogramme, Jena, 1909, p. 29, Fig. 15).

upon observations of the venous pulse, while in rare instances observations upon the activity of the left atrium have been made by means of the œsophageal cardiogram (Minkowski). The electrical examination of the atria is made with the greatest ease and there can be no doubt that the P-wave of the electrocardiogram is synchronous with atrial excitation. In Fig. 27 is reproduced the curve taken from a case of mitral stenosis. The marked accentuation of the P-wave is obvious. It is fully as high as the T wave of the ventricular portion of the curve, which is never the case under normal conditions. Similar observations upon the high P-wave in mitral stenosis were made earlier by Einthoven.

HYPERTROPHY OF THE RIGHT VENTRICLE.

In hypertrophy of the right heart R_1 may be negative and R_3 may be markedly positive (Fig. 28). An interesting case

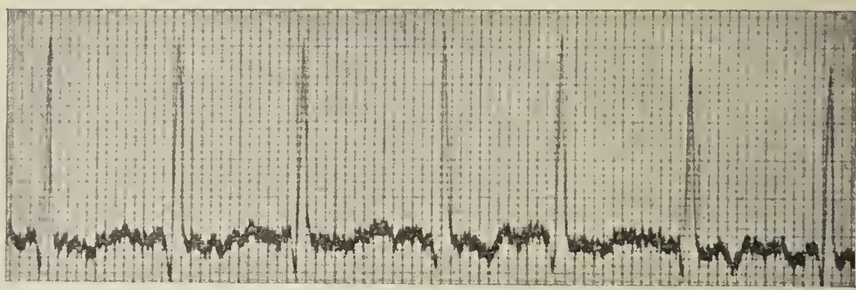


Fig. 28.—Electrocardiogram from case of mitral insufficiency with hypertrophy of the right ventricle; D_3 (after Einthoven (W.), Le Télécardiogramme, Arch. Internat. de Phys., 1906-7, IV, 145, Fig. 17).

of hypertrophy of the right ventricle is recorded with three methods of derivation in Samojloff's article (see his Figs. 20, 21 and 22). It is Einthoven's idea that, in hypertrophy of the right heart where R_3 is very high, the fibres of the conducting system carry the stimuli to the regions which are near the base of the heart, while in hypertrophy of the left heart with a negative R_3 the portions of the ventricle first stimulated by the conducting fibres lie nearer the apex of the heart.

HYPERTROPHY OF THE LEFT VENTRICLE.

Electrocardiograms from cases with hypertrophy of the left ventricle have been made by several observers. An interesting example is that shown in Figs. 29 and 30, taken

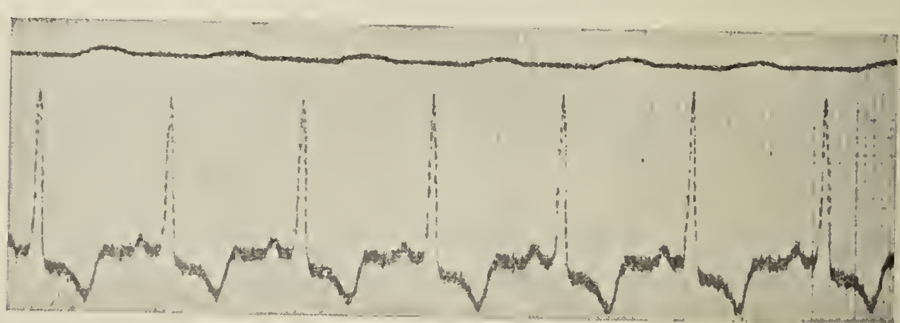


Fig. 29.—Electrocardiogram and carotid pulse from a patient with hypertrophy of the left ventricle due to aortic stenosis; D_1 (after Einthoven (W.), Weiteres über das Elektrokardiogramm, Pflüger's Arch., 1908, CXXII, 569, Fig. 31).

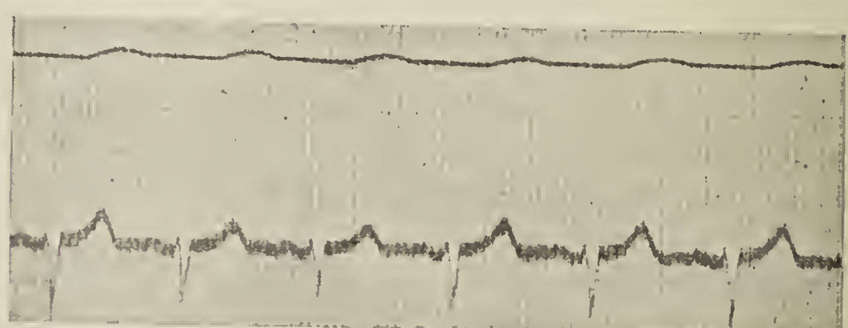


Fig. 30.—Electrocardiogram and carotid pulse in a case of aortic stenosis with hypertrophy of the left ventricle; D_3 (after Einthoven (W.), Weiteres über das Elektrokardiogramm, 1908, CXXII, 569, Fig. 30).

from a patient with aortic stenosis and hypertrophy of the left heart. Here with the first lead R is very high and T is negative, while with the third lead R is negative and T is positive. The importance of multiple derivations is especially well illustrated by these two curves.

In Figs. 18, 19 and 20 of Einthoven's article entitled *Le Télécardiogramme,* the curves from three patients with hypertrophy of the left heart are illustrated. With D_3 all of them yielded a negative R, while with D_1 all yielded a positive R. Similar curves are recorded by Samojloff in his Figs. 17, 18 and 19. R is positive in them with D_1 and D_2 and strongly negative with D_3.

Behavior of the T-wave in myocardial disease.

In curves taken from normal hearts T_1 and T_2 are positive though T_3 may be either positive or negative. In cases of myocardial disease it has been a common finding to obtain curves in which the wave T was very low or even negative with D_1 or D_2 (Fig. 31). Einthoven has expressed the opinion that this finding always indicates a diseased heart though the pathological change may be only myocardial insufficiency or myocardial degeneration. This view has been supported by Kraus & Nicolai and by Samojloff. Recent investigations, however, have shown that a positive T-wave

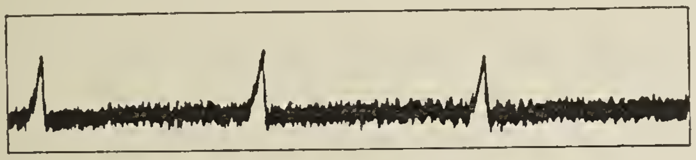


Fig. 31.—Electrocardiogram with loss of T-wave in myocardial disease (after Kraus and Nicolai).

may be present even in severe myocardial disease and in marked myocardial insufficiency (Hoffmann). As yet the exact significance of the T-wave is very obscure.

The atypical electrocardiograms yielded by ventricular extrasystoles.

Among the most interesting electrocardiographic curves obtained clinically are those yielded by hearts in which ventricular extrasystoles occur along with normal systoles. The extrasystolic curve presents a striking appearance in contrast with the typical electrocardiogram, for these atypical curves are produced by large potential differences which continue for a relatively long time. As a rule the electrocardiogram of the atypical heart contraction takes the form of a simple diphasic action-current due to a gradual advance of the excitation wave from one end of the ventricles to the other. The stimulus is not initiated proximal to the ventricles, but evidently begins in the ventricles themselves, sometimes near the base, sometimes near the apex, or probably sometimes in the right ventricle and sometimes in the left. Excellent examples of the curves from such a ventricular extrasystole by all three methods of derivation are shown in Fig. 32. The patient, a woman, A. v. Y., suffered from myocardial degeneration, and in the electrocardiogram of the ordinary beats of the heart the T-wave was sometimes doubled in D_2 (Fig. 32b). The extrasystole yields a wholly different curve from that of the ordinary systoles. There is no evidence of P-, R-, or T-waves, but instead an outspoken diphasic action current making a simple curve of two large waves, one being directed upward and the other downward. In D_1 (Fig. 32a) it is obvious that the origin of the wave is nearer to the right side than to the left side of the heart, while in D_3 (Fig. 32c) the curve indicates that the wave originated nearer the apex than the base. The fact that the two waves are lower in D_2 (Fig. 32b) than in D_1 and D_3 agrees with the assumption that the stimulus originated in the right ventricle near the apex; thence it advanced gradually in a direction toward the left and upward.

Now when the atypical heart-contraction begins near the

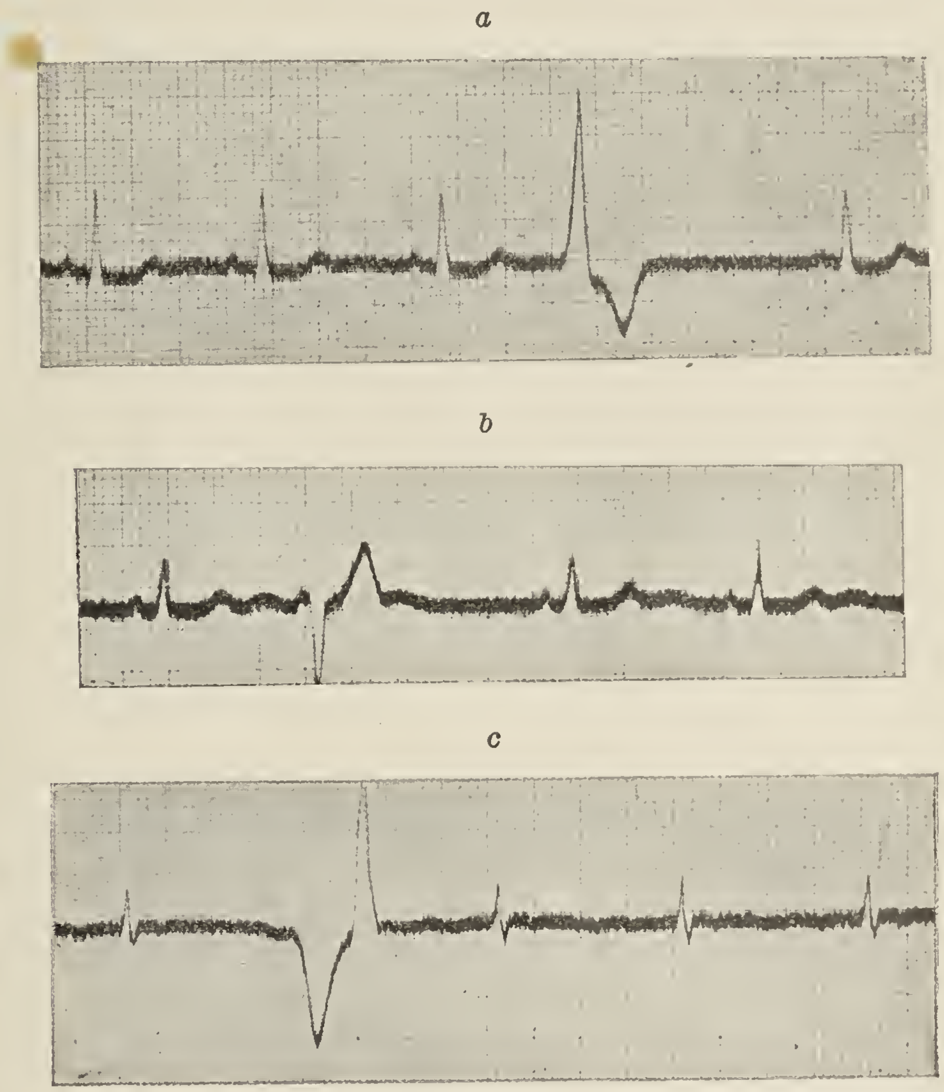


Fig. 32.—a, Curve showing an extrasystole or atypical heart contraction by D_1; b, Curve showing extrasystole or atypical heart contraction by D_2; c, Curve showing extrasystole or atypical heart contraction by D_3. Form of electrocardiogram in ventricular extrasystole or atypical heart contraction by the three principal methods of derivation (after Einthoven (W.), Weiteres über das Elektrokardiogramm, Pflüger's Arch., 1908, CXXII, 579, Figs. 36, 37 and 38 combined into one figure).

base of the heart and advances toward the apex the curves obtained are quite different. In Fig. 33 are reproduced the electrocardiograms obtained from Einthoven's patient S. K., who suffered from a bigeminal arrhythmia dependent upon regularly recurring extrasystoles. In Fig. 33a the curve obtained by D_1 is recorded, while in Fig. 33b that obtained by D_3 is given. For convenience in Fig. 33a an ordinate of 1 mm.$=10^{-4}$ volt, while in Fig. 33b an ordinate of 1 mm.

indicates a potential difference of 2×10^{-4} volt. The waves of the ordinary (normodromic) systoles are designated by the ordinary lettering P, Q, R, S and T. The waves of the atypical (allodromic) curves due to the extrasystoles are small in D_1, which indicates that the wave passed almost directly from the base toward the apex, while the minute elevation at a suggests that at this point the stimulus was probably transmitted from the ventricles to the atria.

There can be no doubt that the path through the heart muscle followed by the stimulus in such extrasystoles is wholly different from the path followed by the stimulus preceding ordinary beats of the heart. Whether the stimulus travels more slowly in such ventricular extrasystoles than in normal systoles is a mooted question. While the curve shows a long duration of the potential differences it is possible, as

a b

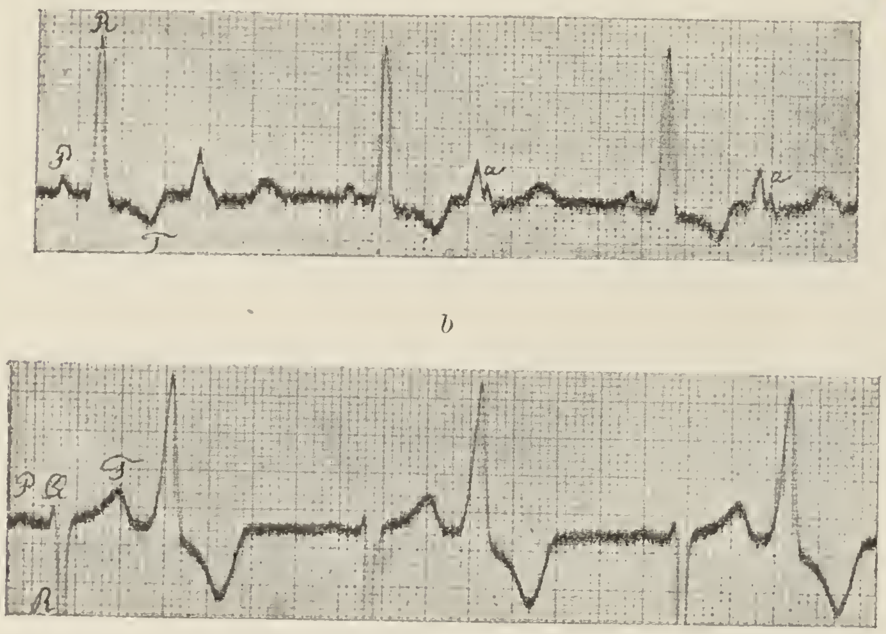


Fig. 33.—*a*. Curve of extrasystole, D_1; *b*, Curve of extrasystole, D_3. Abscissa 1 mm. = 0.04 sec.; ordinate 1 mm. = 2×10^{-4} volt. Forms of curve obtained from extrasystoles by the first and third methods of derivation (from Einthoven (W.), Weiteres über das Elektrokardiogramm, Pflüger's Arch., 1908, CXXII, 581, Figs. 40 and 41 combined into one figure).

Einthoven suggests, that its peculiar extent is due less to slow progress than to the long path which it must follow from the apex to the base or in the reverse direction.

THE TACHYCARDIA OF EXOPHTHALMIC GOITRE AND THE PHYSIOLOGICAL TACHYCARDIA OF EXERCISE.

The first to publish electrocardiograms taken in a case of exophthalmic goitre was, so far as I know, Hoffmann, who found a high T-wave and a shortening of the ventricular portion of the ventricular electrical systole; that is, a lessening of the distance from the beginning of Q or R to the end of T.

We have obtained precisely similar curves in our clinic. The high T-wave is always a marked feature.

It is interesting to compare these curves from pathological tachycardias with the electrocardiogram obtained by Einthoven in the physiological tachycardia due to exercise (Fig. 34). In the tracing taken after exercise the heart is beating more frequently and the atria are stimulated before the ventricular electrical systole of the previous cardiac revolution has been completed, so that one obtains a superimposition of the atrial wave upon the ventricular curve, the former riding tile-like upon the latter. One notices also an enlargement of the P-wave and the T-wave in this physiological

a b

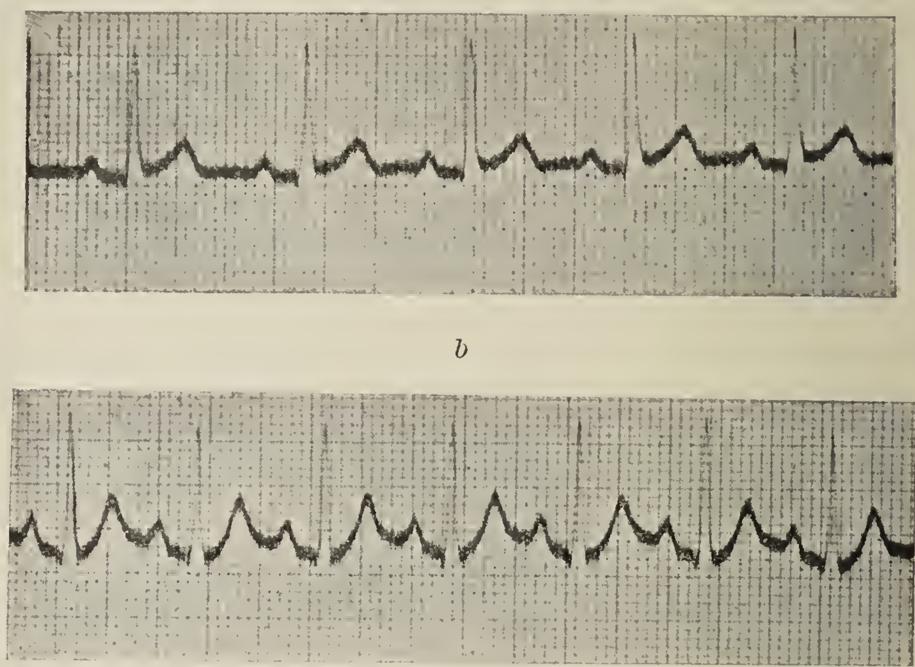


Fig. 34.—*a*, Curve with individual at rest; D_2; *b*, Curve from same individual after violent exertion; D_2. Curves contrastng the form of the electrocardiogram after rest with that after exertion (from Einthoven (W.), Weiteres über das Elektrokardiogramm, Pflüger's Arch., 1908, CXXII, 566, Figs. 26 and 27 combined into one figure.

tachycardia. Q, R and S are also somewhat more distinct than in the same patient at rest, but the changes are less striking than in P and T.

ELECTROCARDIOGRAMS FROM HEART-BLOCK CASES.

One approaches with a high degree of curiosity the records obtained by electrocardiographic methods from patients presenting symptoms of the Stokes-Adams syndrome. Curves of this sort have been recorded by Einthoven (Figs. 2 and 3 of the plate accompanying his article entitled *Le Télécardiogramme,* and Figs. 9 and 10 of Tafel 12 of his article in Bd. 122 of Pflüger's *Archiv*). Several cases of this sort have been studied also by Kraus and Nicolai. Recently we have secured electrocardiograms in Baltimore from a case of complete dissociation of atria and ventricles; the curves will be published in another article. Among the most interesting curves as yet published are those which accompany Pick's article and which I reproduce in Fig. 35. The patient, a man of 43, had three contractions of the atrium to one of the ventricle. The condition followed an acute endocarditis and had been in existence for fifteen years. Though the patient had a pulse rate of 30 he had kept up his work during a large part of this time. At one period he had one hundred and twenty attacks of syncope in twenty-four hours. Gradually the symptoms became less and there had been no attacks during the four years preceding the record here shown. Normal curves by D_1 and D_2 are shown above for comparison, while the curves from the heart-block case with the same two methods

of derivation are figured below. One can scarcely imagine a more beautiful method of demonstrating a complete or a partial dissociation between the activities of the atria and the ventricle. Though the comparative study of phlebograms, arteriograms and cardiograms are quite sufficient for the diagnosis, the mass of waves which one obtains with such records is very complex in contrast with the simplicity and elegance of the demonstration of dissociation which the electrocardiogram affords. In the figures, the atrial waves are indicated as P while the main ventricular wave is marked R. There are three times as many P-waves as R-waves and they bear no regular temporal relation to one another. In one place the ventricular wave coincides in time with the atrial wave (Fig. 35, $P_7 + V_3$). An interesting fact in connection with these curves is the character of the ventricular waves. They are those of the typical electrocardiogram (normodromic) and not those of ventricular extrasystoles (allodromic). It will seem important, therefore, in heart-block cases to recognize the character of the spontaneous ventricular systoles as being wholly different from the ventricular extrasystoles which yield the simple diphasic curves with huge potential differences. It seems likely from this observation alone that the spontaneous systoles of the ventricle in the Stokes-Adams syndrome are initiated in the conducting apparatus close below the line which interrupts the continuity of the atrio-ventricular bundle and the path followed through the heart muscle is that traversed when the heart is beating normally.

As an example of the thorough working up of a case of heart-block by all the newer methods, the reader should consult the report made by Vaquez, Clerc and Esmein (1909).

We have recently had the opportunity, here in Baltimore, of making an electrocardiogram in a case of complete dissociation of the auricles and ventricles in a patient who had suffered but little inconvenience from his cardiac lesion. Though the slow pulse had existed for a long time, he had never had an attack of syncope. When first I saw the patient, a banker from a western State, he had been for some time under considerable mental and physical strain and presented in addition to his slow ventricular rhythm (normodromic beats) a large number of ventricular extrasystoles (allodromic beats). With rest in bed and a quiet environment these extrasystoles quickly disappeared, and when the electrocardiogram was taken one got only the P-waves of the atrial rhythm and the R- and T-waves of the dissociated spontaneous ventricular rhythm. It was surprising how well the patient got along in spite of his heart-block. Ordinarily ventricular extrasystoles are of litttle help in the mechanical work of the heart, but it seems probable that in certain heart-block cases the allodromia may prevent syncopal attacks.

In health, during increased work, the rate of the heart is

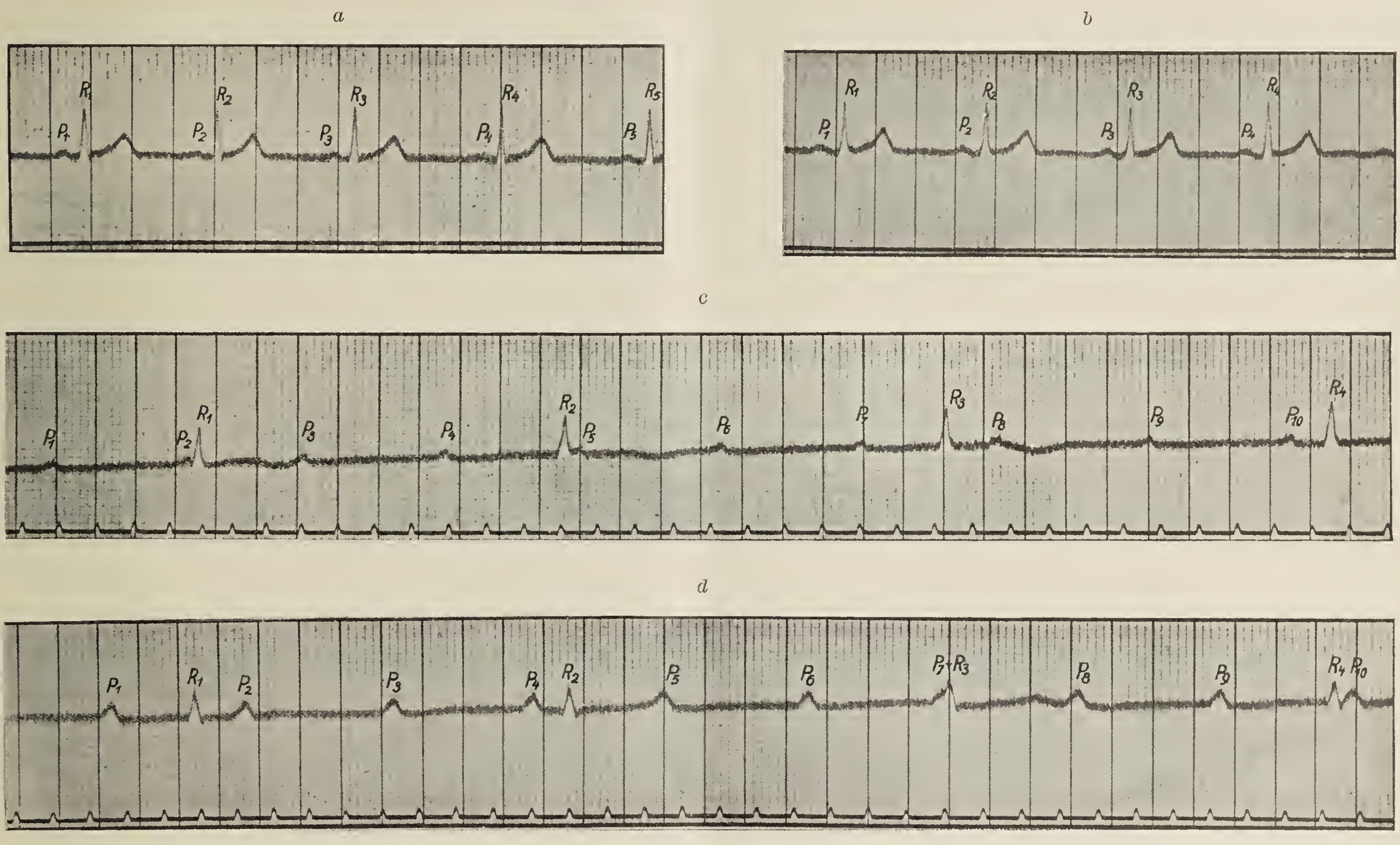


FIG. 35.—Pick's heart-block case. a, normal curve D_1; b, normal curve D_2; c, Case N. D_1; d, Case N. D_2.

increased through the action of the accelerator fibers upon the sino-auricular node of Keith and Flack, but in heart-block the rhythm of the ventricles cannot be increased either directly through the accelerators or indirectly by the transmission of the impulses from the sino-auricular node through the His bundle to the ventricles. On the contrary, the simultaneous exaggerated innervation of the antagonistic N. vagus may tend somewhat to slow the rate of the ventricles. It may be that this stimulation of the vagus favors the irritability of the tertiary auxiliary excitation points, perhaps at the termini of Tawara's conduction system in the ventricular walls, and so permits of compensatory extrasystolic beats. Such an explanation has been offered by Nicolai in a case similar to the one I have mentioned above. In Fig. 36 is represented Nicolai's diagram illustrating his ideas of the re-

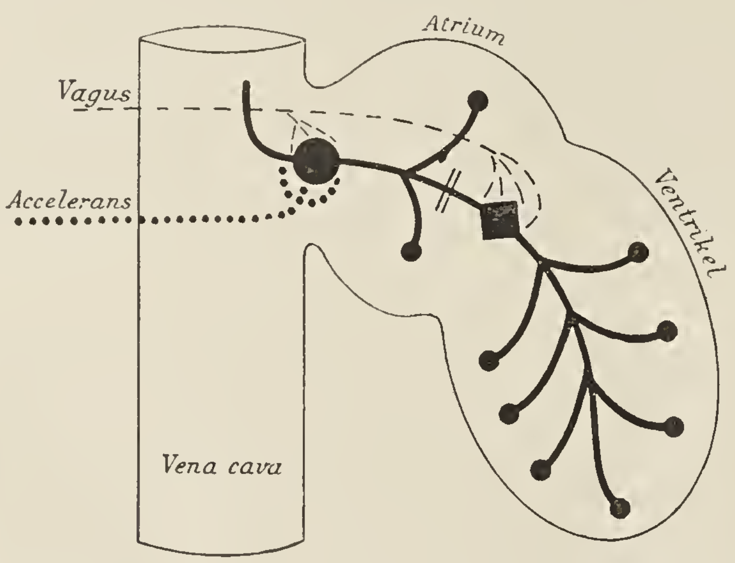


Fig. 36.—Scheme of the cardiac centers of the conduction system and the points upon which the extra-cardial regulatory nerves act (after Nicolai (G. F.), Deutsche med. Wchnschr., 1909, II, 2254, Fig. 1). ○, primary automatic rhythm center (Keith-Flack sinus node). □, secondary rhythm center (Aschoff-Tavara atrio-ventricular node). o, Tertiary centers (heart ganglia or musculature).

lations of the N. accelerans and the N. vagus to the primary (normal), secondary (vicarious) and tertiary (auxiliary) centers of cardiac excitation. In Fig. 37 are shown the electrocardiograms in Nicolai's case before and after work.

Of unusual interest in this connection are the hæmodynamic observations of Plesch. As students of cardiac pathology know, this investigator has worked out a method for measuring clinically the minute-volume of blood given out by the left ventricle. On the average in normal individuals this minute-volume amounts to four liters or about 60 cc. per systole when the body is at rest. During work twenty times as much may be needed and the increased minute-volume can be obtained either by increased systolic output or by a more rapid rate of the heart.

In Nicolai's case of heart-block the single systolic output was very large, amounting to 174 cc. instead of the normal 60 cc. The size of this output was doubtless related to the small number of systoles and was perhaps in part dependent upon the fact that the patient was anæmic, so that a normal minute-volume of four liters was insufficient for the oxidation-processes of the body. The minute-volume, as calculated by Plesch, amounted in this case to 7.6 liters. When this patient tried to work, the usual methods to which the heart resorts for increasing the minute-volume were not available; the frequency of the heart beat could not be increased in the ordinary way and the single systolic output had reached a maximum at rest. Ordinarily, therefore, one would expect that such a man, if he exerted himself, would suffer from the collapse of the typical Adams-Stokes syndrome. Syncope did not occur and the reason probably lay, as in my patient, in the development of the extrasystoles, whose systolic outputs, added to those of the more normal contractions, sufficed for the cerebral oxygen-supply. If these views are correct we

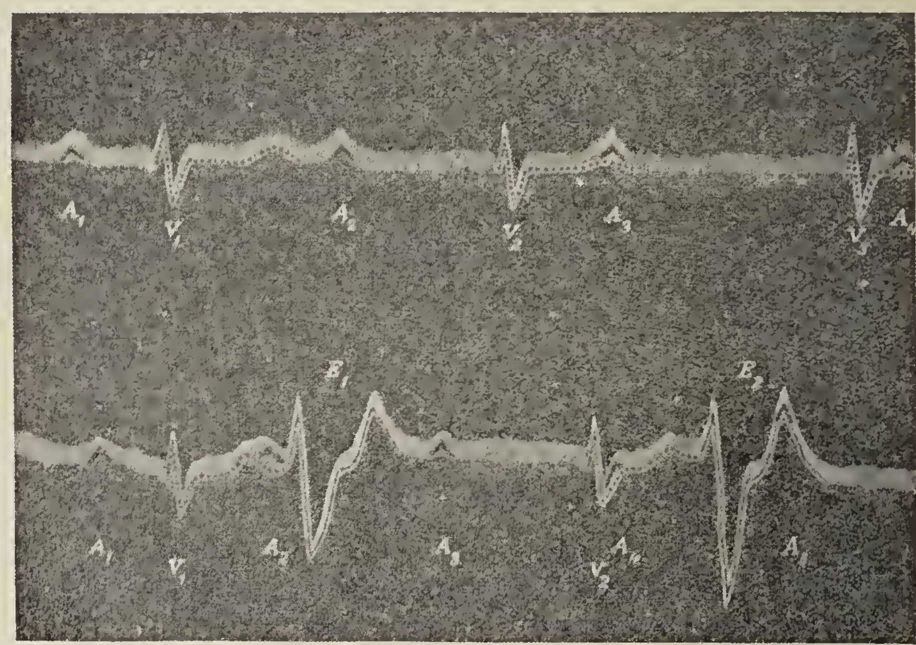


Fig. 37.—Electrocardiogram before (*I*) and after (*II*) work in a case of heart-block (after G. F. Nicolai). A = atrium contraction; V = ordinary ventricular beat (normodromic systole of secondary center); E = extrasystole (allodromic systole from tertiary center).

Curve I	40 A	32 V		per minute.
Curve II	65 A	26 V	26 E	per minute.
		52		

i. e.: A at rest = A at work = 4.
V at rest = V at work = 5.

Only a part of the original figure has been reproduced.

must recognize that extrasystoles may sometimes exercise a most important compensatory function.

CONGENITAL HEART DISEASE.

Curves from congenital heart disease showing peculiar R-waves and T-waves have been published by Einthoven (see Fig. 24 of his *Le Télécardiogramme* and Fig. 35 of his article in Pflüger's *Archiv*, Bd. CXXII). I shall not reproduce them here inasmuch as the exact nature of the congenital disease does not seem to have been clearly made out. Only where the clinical study has been controlled by autopsy could such curves have much value.

The same comment applies to Wandel's report of curves taken in a case of persistent Ductus Botalli; here, instead of a single R-wave, the initial ventricle-variation was multiple!

ATRIAL PARALYSIS AND ARHYTHMIA PERPETUA.

Those who have worked with phlebograms and arteriograms have been much interested during the past few years in the study of cases in which the atria are paralyzed and in which the pulsus irregularis perpetuus exists. It seems that the pulsus irregularis perpetuus is sometimes accompanied by paralysis of the atria, though not always. We have repeatedly taken curves from a patient under our observation at the Johns Hopkins Hospital, in which the perpetually irregular pulse was accompanied by atrial paralysis. One notes in the electrocardiograms the absence of the *P*-wave though *R* and *T* are well marked. The *R-R* interval shows remarkable variations in time. We have been able to observe cases in which atrial paralysis existed for a time (absence of *P*-wave) to disappear later (return of *P*-wave). Investigations of similar cases have been made by Einthoven (1906-07), Kraus and Nicolai (1907), Hering (1908) and by Rothberger and Winterberg (1909). These electrocardiographic studies

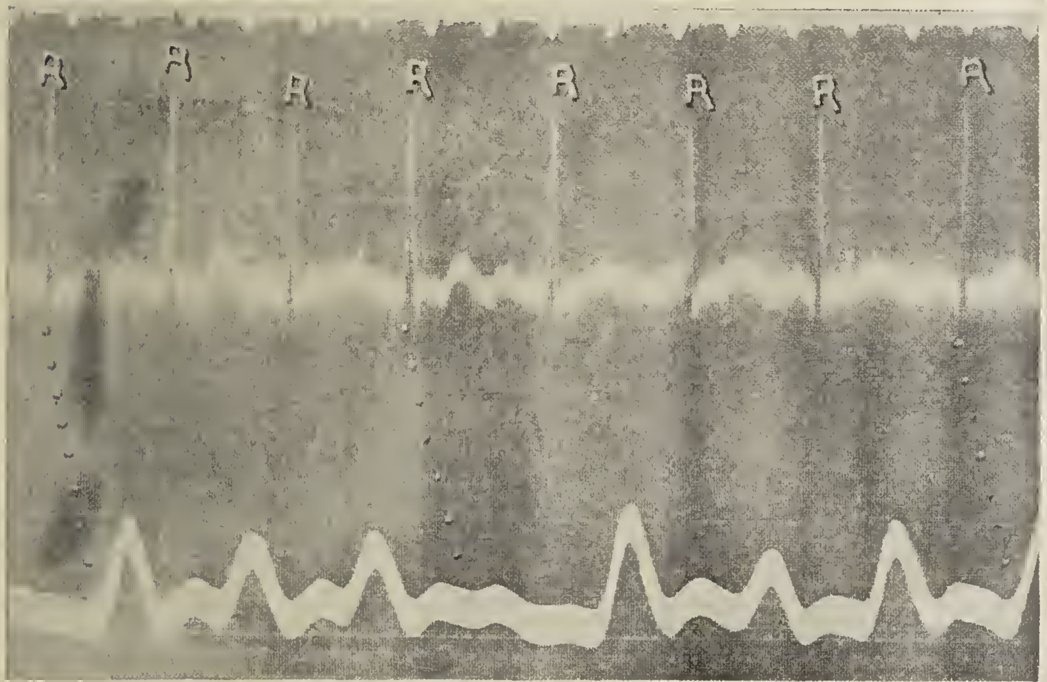


Fig. 38.—Electrocardiogram from a case of paroxysmal irregularity. The *P*-wave is absent and the *R-R* interval varies (after Thomas Lewis, Heart, 1910, I, Fig. 15). Only a part of the original figure is reproduced.

seem likely to bring the proof that in some of these cases fibrillation of the atrium exists (*vide infra*). The experimental investigations of Cushny and Edmunds, together with the electrocardiographic studies of Rothberger and Winterberg and of Lewis (1909-1910), promise to throw much new light on what has hitherto been a dark portion of cardiac arhythmia.

According to Kraus, electrograms indicate, in pulsus irregularis perpetuus, (1) the presence of groups of beats with falling or rising rhythm; (2) often combinations with atypical heart-beats due to stimuli abnormally located, though these atypical beats are less often ventricular extrasystoles than beats arising from stimulation of the Aschoff-Tawara node in the His bundle at the atrio-ventricular junction.

Lewis in London has recently (November, 1909) reported electrocardiographic observations upon atrial fibrillation. He, like Rothberger and Winterberg, believes it to be the cause of the pulsus irregularis perpetuus. The electrograms taken show, in addition to the *R*- and *T*-waves of the ventricular excitation, numerous small irregular elevations throughout the *T-R* interval (*i. e.*, between two ventricular excitations), which correspond to similar irregular waves obtained in animals in experimental atrial fibrillation. He suggests that James Mackenzie's nodal bradycardia may be a complete heart-block associated with fibrillation of the atria.

In a still later paper published in *Heart* (March 30, 1910), Lewis gives a very complete review of the whole subject based upon curves taken from thirty cases. In Fig. 38 a part of one of the characteristic curves is reproduced.

HEARTS OF NEURASTHENIC PATIENTS.

A very careful study of a large number of the out-patients in the neurological clinic in Berlin has been made by Nicolai and Simons. It has been suggested that the wave *S* of Einthoven (Nicolai's *Jp*) is especially marked in neurasthenic individuals, and Kraus had actually referred to it as the *nervöse Zacke*. Kraus had found this wave present not only in hypertrophic hearts, but in the hearts of children and young adults, especially in young females. Most of these patients presenting the marked wave were infantile or feminine and had labile vasomotors, indicating a predominance of the sympathetic activities over those of the regulators such as the vagus. The studies of Nicolai and Simons, however, have proved that many neurasthenic patients show no abnormality of the wave *S*.

HEARTS OF INFANTS.

It is interesting that Funaro and Nicolai found the *S*-wave (the so-called neurasthenic wave) well marked in forty-five sucklings from whom they took electrocardiograms! They think it possibly due in these infants to slight dislocation of the heart owing to a high position of the diaphragm. This peculiarity of the infantile electrocardiogram is said to disappear after the first year of life, except in children suffering from retarded development, in whom it may persist longer.

PAROXYSMAL TACHYCARDIA.

Electrocardiograms taken during an attack of paroxysmal tachycardia have been published by Hoffmann (1909) and also by Lewis (1909). The curves obtained by Lewis are particularly interesting and confirm his view that two fundamentally different forms of paroxysmal tachycardia exist, one (a) characterized by the persistence during the paroxysm of the presystolic contraction of the atrium (*atrial* or *auricular form*) and the other (b) by the absence of atrial contraction in the presystole, the atrium in reality contracting simultaneously with the ventricle or a little later (*nodal* or *ventricular form*).

Lewis has succeeded in producing a ventricular form of paroxysmal tachycardia in dogs. After severing all the nerves connecting the heart with the rest of the body, the paroxysm of tachycardia can be started by simply ligaturing the descending branch of the left coronary artery, or better still,

the trunk of the right coronary. In the tachycardia produced the ventricles contract first and the atria later, so that the form is ventricular (though not nodal).

GALLOP-RHYTHMS.

Rothberger of Vienna has studied electrocardiograms from a patient manifesting gallop-rhythm. The curves resemble so strikingly the curves obtained from experimental animals in which one branch of the His bundle has been cut below Tawara's node that this author is inclined to look upon gallop-rhythm as an evidence of univentricular conduction-system disturbance.

ELECTROCARDIOGRAMS IN EXPERIMENTAL WORK.

The effects of rest, of exercise and of dislocation of the heart by the distended stomach, by pleural effusions and by mechanical means, have been studied especially by Hoffmann and by Einthoven, and some of the results obtained have been referred to above.

A number of observers, too, have worked upon the exposed heart of animals, leading off the currents directly from atrium or ventricle and attempting to throw light upon the normal electrocardiogram obtained by leading off from the extremities. Of the other experimental researches may be mentioned the effects upon the electrocardiogram of experimental hæmorrhage, of intoxications, of vagus stimulation, of injuries to the heart muscle (thermal, chemical, mechanical, electrical) and of fibrillation of the atria and ventricles.

HÆMORRHAGE.

The main effect of hæmorrhage on the electrocardiogram of the dog is a lowering of the *T*-wave, perhaps due to the lowered blood pressure (Einthoven). According to Kahn (1909) this lowering occurs only after some little time has elapsed; this author describes the series of changes in the electrogram which follow hæmorrhage due to section of the abdominal aorta.

CHLOROFORM POISONING.

The effects of chloroform poisoning have also been studied by Einthoven. The main effect is seen in the wave *T*, which is changed and may often be negative. In deep narcosis chloroform lengthens the *A-V interval* (that is, the lengthening of time between the end of *P* and the beginning of *Q* or *R*). If the chloroform be pushed still farther the activities of the ventricles and the atria may be partially or completely dissociated and extrasystoles may appear, yielding atypical electrocardiograms. These effects are all markedly increased if the vagus be stimulated during the administration of the anæsthetic. Einthoven suggests that later on surgeons may come to use the string galvanometer during anæsthesia in order to keep tab on the heart.

OTHER INTOXICATIONS.

Among the other poisons whose effects upon the electrocardiogram have been studied are strophanthin, digitalis, muscarin, adrenalin, diphtheria toxin and yohimbin. Work with these poisons has really only been begun and it is too early as yet to speak with any certainty regarding them. The details will be found in the publications of Kraus and Nicolai, Lewandowsky and Strubell.

VAGUS EFFECTS.

Very interesting observations upon the effects of vagus stimulation have been made by Gaskell, Gotch, Einthoven and H. E. Hering.

Cutting the vagus increases the rate of the heart owing to the loss of vagus tonus. In such a tachycardia the electrical waves due to the ventricle are not yet over when the next atrial wave begins, so that the atrial wave becomes superimposed upon the end of the preceding ventricular wave. Analyzing Einthoven's results one finds that the waves *Q* and *R* are very little altered, that *T* becomes a little smaller, *S* somewhat larger on cutting the vagi, but far the most important change is that in the wave *P*, which becomes almost three times as high as in the uninjured animal.

Another effect of section of the vagi is shortening of the heart pauses due to the tachycardia. The duration of the potential change in the atrium is very little altered, but the *A-V* interval is much diminished; in a normal animal it amounted to 0.13 seconds, while in an animal with cut vagi it was only 0.09 seconds. The *R-T* interval in the animal with uninjured vagi was 0.16 seconds, in the dog with sectioned vagi 0.13 seconds. In sum, then, the loss of vagus tonus leads to greater potential differences in the atrium, less potential differences in the ventricle, a slight shortening of the time of the atrial potential difference, a greater shortening of the time of ventricular differences and a shortened conductivity of impulse in the tissue between the atrium and the ventricle.

In contrast with these effects resulting from section of the vagi are those obtained by variable grades of stimulation of these nerves.

In Einthoven's experiments two striking effects of feeble stimulation of the vagus of the dog were observed; namely, lengthening of the heart pause with bradycardia, and decrease in the size of the *P*-wave. In addition to these two principal changes there was a slight increase in the distance between *R* and *T*.

On stronger stimulation of the vagus, sufficient to cause arrest of the heart, Einthoven observed a very marked effect upon the atrial electrogram. Sometimes the *P*-wave is simply diminished in height without undergoing marked change in form, but in other instances the form of the wave is much modified; instead of a single elevation above the zero line with fall again to that line, one sees a curve which falls below the abscissa after the wave to rise again thereto before the *R*-wave appears. One notices also a little lengthening of the time of the potential difference in the atria and also a slight lengthening of the *P-R* interval.

Sometimes a complete dissociation between the atria and ventricles results from strong vagus stimulation and this, together with a fall of blood pressure during the block, is well shown in Fig. 39. The peripheral end of the right vagus which had been cut through was stimulated by induction cur-

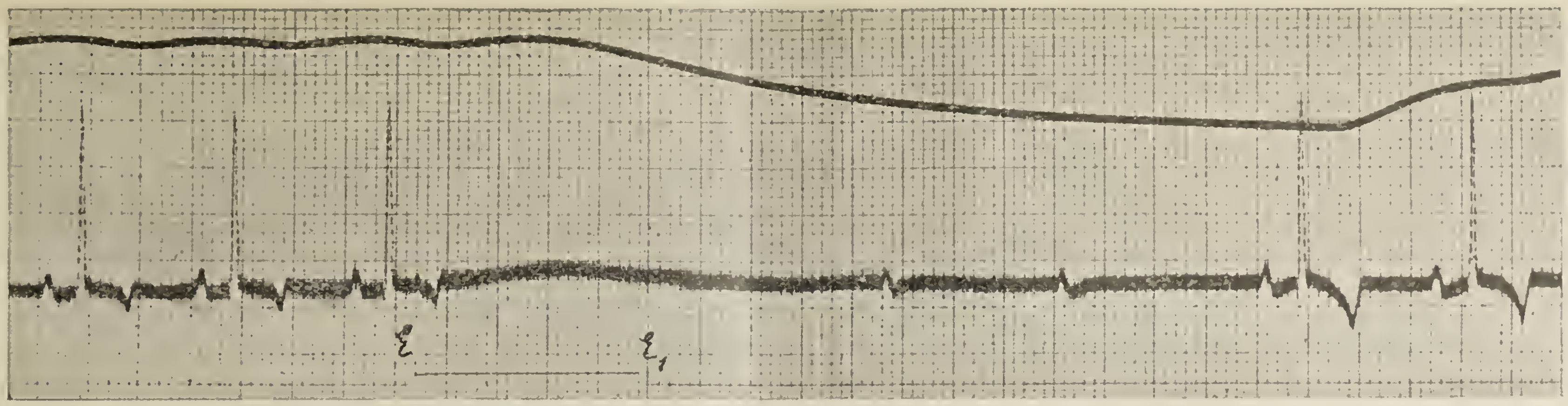


Fig. 39.—Effect of vagus stimulation upon the blood pressure curve and electrocardiogram in the dog; D_2 (after Einthoven (W.), Pflüger's Arch., 1908, CXXII, Taf. 11, Fig. 2). The vagus stimulation began at E and ended at E_1. Only a part of the original figure is reproduced.

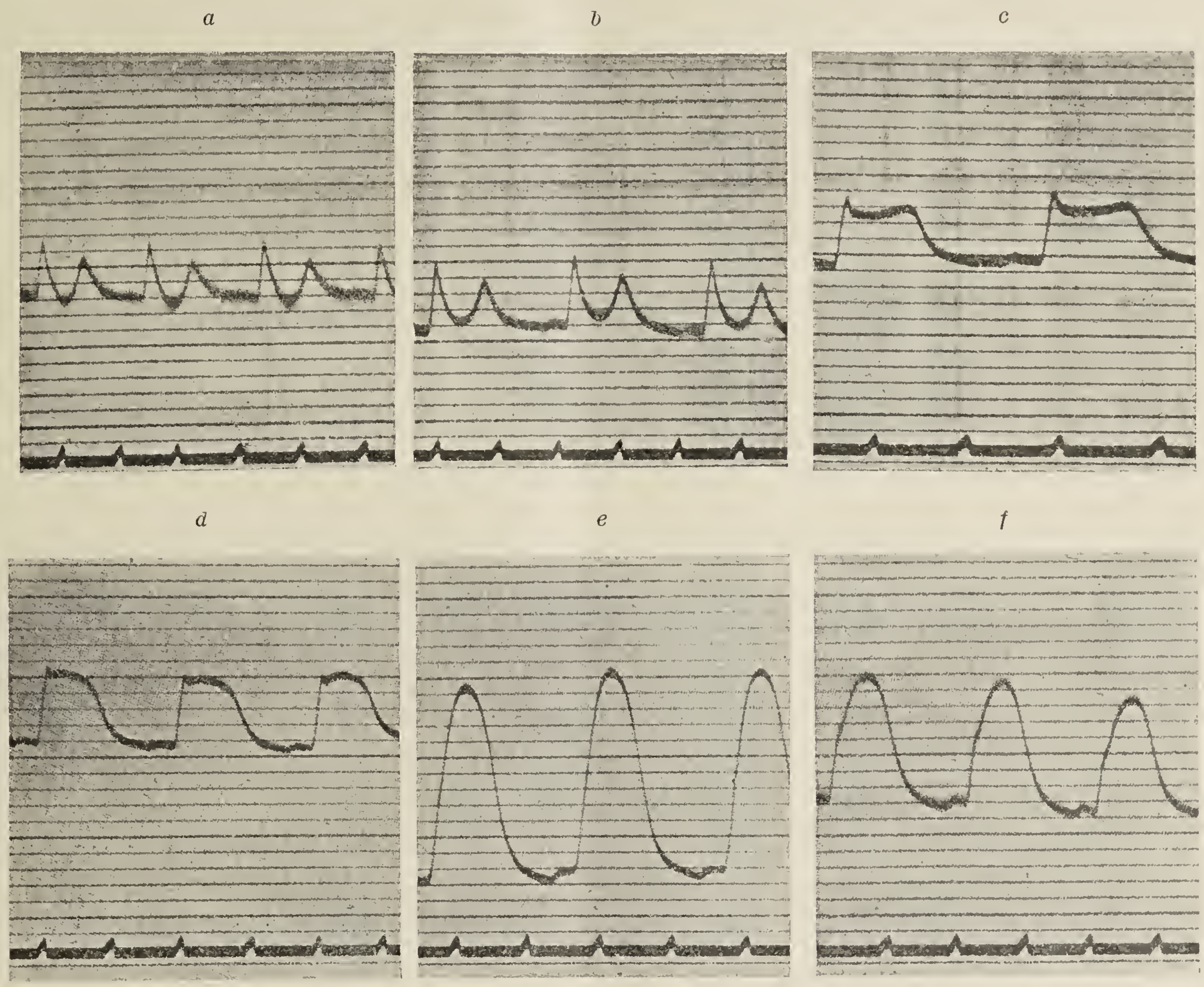


Fig. 40.—Electrocardiogram showing effect of destruction of portion of wall of left ventricle in the dog (after Eppinger and Rothberger, Wiener klin. Wchnschr., 1909, XXII, 1093).

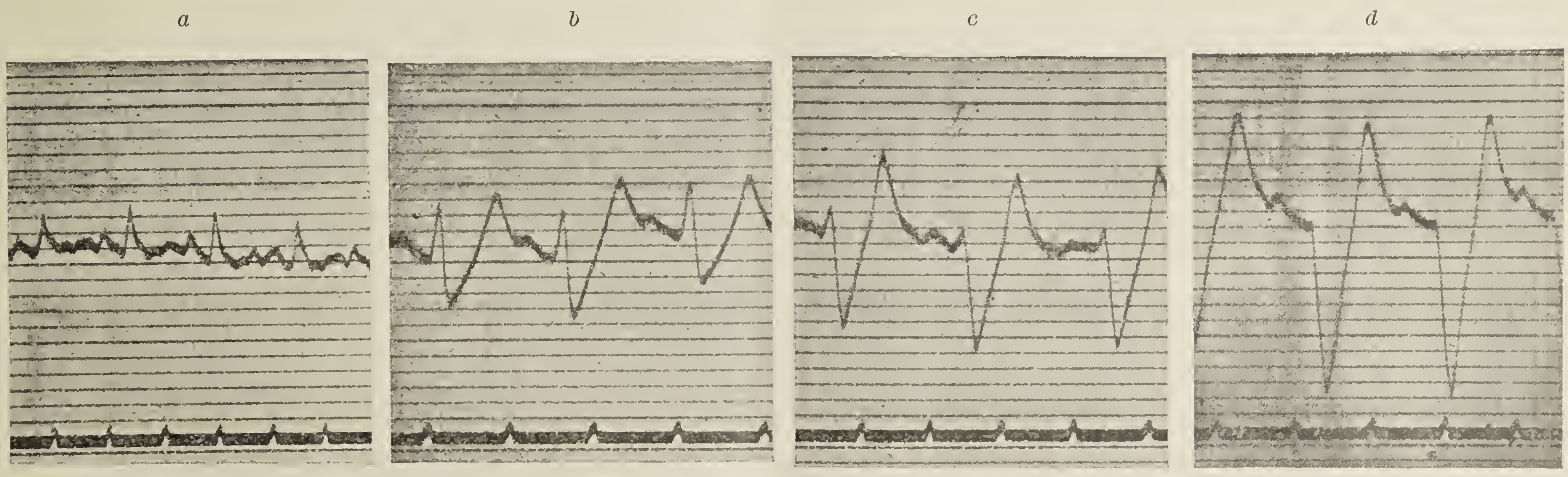


Fig. 41.—Electrocardiogram showing the effect of destruction of portion of wall of right ventricle in the dog (after Eppinger and Rothberger, Wiener klin. Wchnschr., 1909, XXII, 1094).

rents between E and E_1; blood pressure fell from 130 to 32 mm. of mercury; there was at first complete arrest of both atria and ventricles, followed by two atrial excitations which have no corresponding ventricular excitation; after this the regular sequence of atrial and ventricular excitation reappears. In the recovery from arrest of the heart from strong vagus stimulation the atria behave entirely differently from the ventricles. The atria evidently recover gradually, while the ventricles follow the "all or nothing" law. When the ventricular excitations begin the potential differences of the ventricles are as large as normal while those of the atria are still smaller than normal.

These results of Einthoven have recently (1909) been largely confirmed and somewhat extended by H. E. Hering.

INJURIES TO MYOCARDIUM.

Attempts have been made to injure various portions of the myocardium in order, if possible, to interrupt the course of the impulses through the heart muscle and so to modify the form of the electrocardiograms. Eppinger and Rothberger, by means of a cooling spray, froze different foci in the two ventricles and obtained certain modifications of the R- and T-waves. They also injected sublimate and silver nitrate by means of a long needle into the heart, causing necrosis, and got interesting modifications of the curve.

The immediate effect of the injection was a shower of extrasystoles, but in one or two minutes a stationary condition usually resulted. Occasionally death occurred from fibrillation of the ventricle.

In injuries to the left ventricle the main thing they discovered was that descent of the R-curve was made more difficult or hindered altogether (Fig. 40). The normal curve is shown at a, while at c the valley between R and T has almost disappeared. The authors got this effect thirteen times in twenty-five injections into the left ventricle. The results were the same whether they injected at the base or at the apex and the effect could never be produced by a superficial lesion or by injury to the papillary muscles.

Injections into the right ventricle yielded more variable results. The extreme effect is shown in Fig. 41. In a there is a fairly normal curve though the T-wave is split. In b the R-wave is larger and there is a large S-wave followed by a very large T. In c and d the changes are still greater; S and T have grown larger and R has finally disappeared and they got a curve like that of an extrasystole arising in the left ventricle (d). This curve differs from that of a ventricular extrasystole, however, since the P-wave is present. The effects produced by injuring the two ventricles are just opposite to one another.

On injection into the septum it made no difference whether the site of the injection were near the apex or near the base, but it made a great difference whether the site selected was midway between the two surfaces of the septum or nearer the interior of one of the ventricles. When the middle of the septum is injured the lesion resembles that due to injury of the left ventricle.

In general, Eppinger and Rothberger were struck by the fact that in these myocardial injuries sometimes very large foci had no effect upon the form of the curve, while in other instances very small foci had a marked effect. These differences were probably due to the degree in which the conduction-system in the heart was involved in the lesions. They subsequently tried cutting single portions of the conduction-system in curarized animals. Their curves obtained from section of the left and right branches respectively of the ventricular portions of the His bundle are reported to be very remarkable. These observers assert that on section of the left branch they got an atypical electrocardiogram similar to that of an extrasystole originating in the right ventricle, and on cutting the right branch an atypical electrocardiogram similar to that yielded by an extrasystole originating in the left ventricle, but in contrast to the atypical electrocardiograms yielded in man by ordinary extrasystoles the curves always presented, in addition, an atrial wave which was unaltered. On listening over hearts with one branch of the His bundle cut, they heard sounds resembling those of gallop-rhythm, and they hint that gallop-rhythm in man may depend upon injury to one or the other branch of the His bundle. They have obtained a similar curve from a patient during life; the man was studied during several months and presented a constant form of electrocardiogram. At autopsy a large myocarditic focus was found in the septum and the naked-eye examination revealed apparently an interruption of the right branch of the bundle; the microscopic study has not yet been reported.

It is interesting that in experimental block, due to section of the His bundle, vagus stimulation causes slowing of the atrial rhythm, but has no effect, they assert, upon the spontaneous rhythm of the ventricle. Nicolai, on the contrary, finds some slowing of the ventricle in complete heart-block in human beings when the patient works; here the N. accelerans, being stimulated, hurries the rate of the atria, while simultaneous stimulation of the antagonistic N. vagus slows the dissociated ventricles and sometimes brings out compensatory ventricular extrasystoles (*vide supra*).

EXPERIMENTAL PULSUS ALTERNANS.

A good deal of experimental work has been done in the last few years upon the production of disturbances of contractility of the heart as manifested in the form of pulsus alternans. One of the methods of producing this change in contractility consists in the administration of glyoxylic acid. In animals so intoxicated Hering has taken electrocardiograms; he found the typical form though the waves were low; in other words, in pulsus alternans we have, during the feeble systole, to deal, he believes, merely with a hyposystole, produced through stimulation of the regular conduction-system, not with a ventricular extrasystole. In the feeble systole the electrical changes may be large when the effects seen in mechanical registration are small. The waves R and T may be both affected or either one may be more involved than the other.

EXPERIMENTAL EXTRASYSTOLES.

These have been studied with the aid of the string galvanometer by Einthoven, Nicolai, and especially recently by Kahn. Extrasystoles may be atrial, fascicular or ventricular in origin. To summarize the results of these studies it may be said that artificial stimuli applied to the walls of the ventricle of experimental animals yield atypical electrocardiograms. In other words, the contractions resulting from such stimulation correspond more or less closely to those of extrasystoles, which occur spontaneously, rather than to those of normal heartbeats. Kahn found that stimulation of the base of the right ventricle and of the apex of the right ventricle yield very similar curves, while stimulation of the apex of the left ventricle yields a curve in which the waves are in the opposite direction. There is a tendency, therefore, at present to assume, that in extrasystoles yielding atypical electrocardiograms, if the first wave be up and the second down the origin is to be looked for in the right ventricle, while when the opposite is the case (first wave down and second wave up) the source of the extrasystole is to be sought in the left ventricle. The subject, however, needs further experimental study, since extrasystoles occurring spontaneously in man may conceivably have their origin in stimuli arising near the endocardium, while in experimental animals the electrical stimulus has, as a rule, been applied to the external surface of the ventricles.

The idea that there are uniform types of electrocardiograms of extrasystoles arising in the right and left ventricle respectively is combated by good observers (Kraus and Nicolai; T. Lewis) on the ground both of observations on human beings and of animal experiments. The form of the atypical curve obtained depends, Lewis believes, much more upon the phase of diastole in which the extrasystole originates, and a form thus arising may be further complicated by the superimposition upon it of a curve due to a normal excitation. An extrasystolic curve is identical in length, he asserts, with the curve of a normal excitation. He finds that there are a series of special varieties of electrocardiogram each corresponding to excitation of the atrium in a particular region. Thus he got different kinds of *P*-waves, that arising on stimulation of the vena cava superior resembling most closely the *P* of typical electrocardiograms.

The ventricular contractions which follow upon extra beats of the atrium (so-called auricular extrasystoles) vary according to the particular time in ventricular diastole in which the excitation impinges upon the ventricle; the *R*-wave is often altered and the *T*-wave is inverted if at the beginning of diastole or diminished at the end thereof. The interval between *P* and *R* is often prolonged in the precocious auricular extrasystole. Lewis emphasizes the constancy of form of extrasystoles when observed for months in the same individual, a fact which points, in his opinion, (1) to a constant cause, and (2) to a small myocardial area in which the abnormal influence is felt.

Kraus and Nicolai have maintained that the ventricular electrocardiogram following upon an auricular extrasystole differs according as the extrasystole has been produced experimentally in the right atrium or in the left atrium.

FIBRILLATION OF THE ATRIA AND VENTRICLES.

The important facts previous to electrocardiographic studies regarding fibrillation of the atria are summarized in Hirschfelder's article published in this Bulletin in November, 1908. An electrocardiogram of the ventricles in fibrillation was taken by Kahn in 1909 (Pflüger's *Archiv*, Vol. 126).

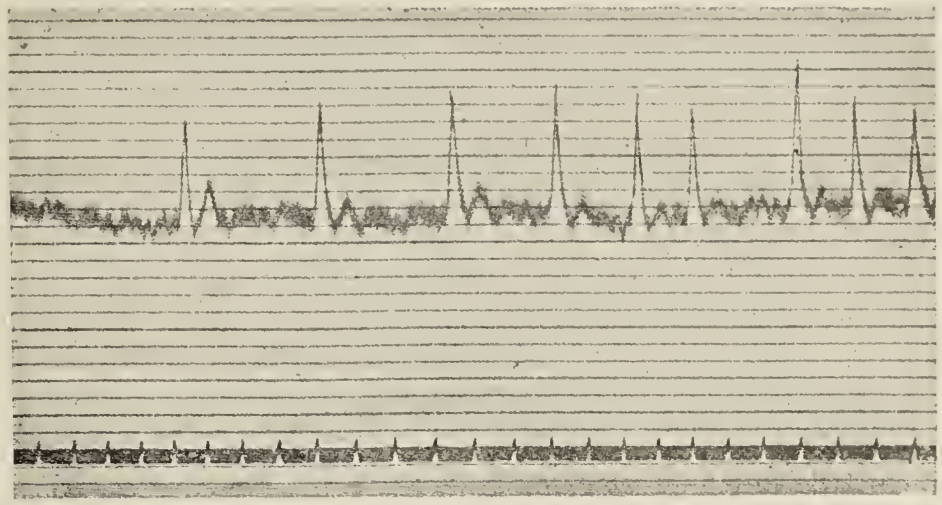


Fig. 42.—Electrocardiogram from experimental fibrillation of the atrium in the dog. The pulse has the characters of the pulsus irregularis perpetuus in man (after Rothberger and Winterberg, Wiener klin. Wchnschr., 1909, XXII, 841, Fig. 1).

In the same year Rothberger and Winterberg, using curarized animals, found that a brief faradic stimulus of two or three seconds, combined with vagus excitation, would cause fibrillation of the atria which would last for some time or even remain permanent. Toxic stimulation of the vagus with drugs like pilocarpin, nicotin, physostigmin or muscarin also caused atrial fibrillation. Electrocardiographic curves made by D_2 showed complete absence of the *P*-wave and a tremor of the string all through the resting intervals. The *R*-wave was free from the tremor, though the *T*-wave sometimes showed it. In Fig. 42 a characteristic arhythmia shown by the variable length of the *R-R* intervals is observable; the *P*-wave is absent; the *T*-wave is distinct. In the pauses larger and smaller waves, which the authors think due to fibrilla-

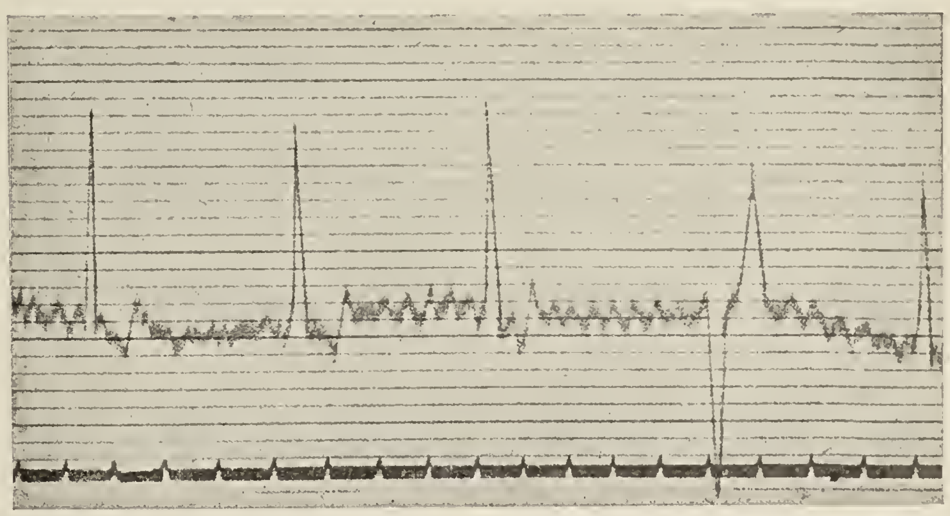


Fig. 43.—Electrocardiogram showing coarser form of curve sometimes obtained in experimental atrial fibrillation (after Rothberger and Winterberg, Wiener klin. Wchnschr., 1909, XXII, 842, Fig. 4).

tion, can be made out. The coarser form of atrial fibrillation is represented in Fig. 43. The authors also show curves from two patients with permanent arhythmia; the tracings in their opinion prove the presence of atrial fibrillation.

The most elaborate study of atrial fibrillation thus far made is that of Thomas Lewis (1910). Rendering dogs insensitive with morphin and paraldehyd as well as by deep surgical anæsthesia he produced fibrillation of the atrium by faradic stimulation of one auricular appendix. He drew off the currents from the heart in different ways. The oscillations obtained were unique, occurring in no other experimental condition. They are illustrated in Figs. 20 and 22 accompanying his article in Vol. I, No. 4, of *Heart*. The variations of the current succeed each other rapidly at a rate of from 500 to 900 per minute. They replace the *P*-wave of a normal curve and distort the *T*-wave in the same way as that already seen in curves of pulsus irregularis perpetuus in man. The waves continue throughout the whole of the cardiac cycle. These waves are present only when the atrium is in fibrillation and they disappear entirely in the same animals if the normal rhythm becomes re-established. It would seem that Lewis, on the one hand, and Rothberger and Winterberg, on the other, have arrived at almost identical results independently of one another.

THE WAVES OF THE ELECTROGRAM AND INTRACARDIAC PRESSURE.

The relation of the waves of the electrogram to events in the cardiac cycle in the dog has been studied by Kahn (Fig.

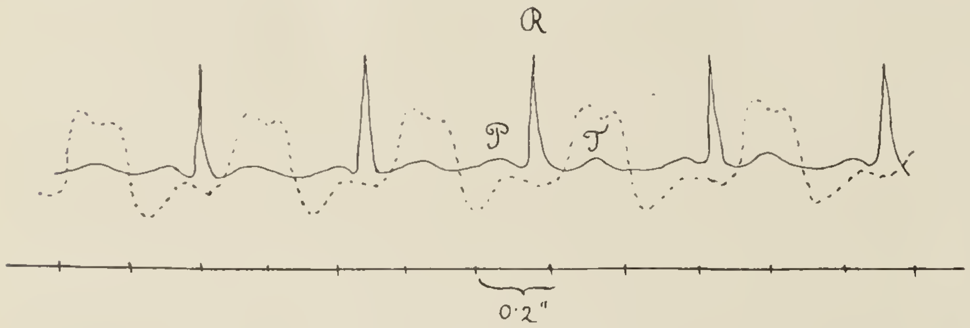


Fig. 44.—Scheme showing the relation of the waves of the electrocardiogram to the curves of intra-ventricular pressure in the dog (after R. H. Kahn, Pflüger's Arch., 1909, CXXVI, 209, Fig. 16).

44). He finds that the *P*-wave coincides with or precedes slightly the apex of the curve of intra-atrial tension. The wave *R* is produced just before the beginning of ventricular activity and disappears during the tension-time; it is all over at the beginning of the expulsion-time. The *T*-wave, on the contrary, occurs during the expulsion-time; it is synchronous with the plateau so often seen on the curve of intraventricular pressure. On making cardiophonograms simultaneously with electrocardiograms, Kahn finds, in the dog, that the first sound of the heart occurs in the interval between *R* and *T*; it begins synchronously with the ascent of the curve of intraventricular pressure, just at the moment when the *R*-wave ceases, and the sound is over a little before the *T*-wave appears. The second sound of the heart begins about one-twentieth of a second after the end of the *T*-wave.

Interpretation of the Typical Electrocardiogram.

Various attempts have been made to explain the form of the electrocardiogram on the basis of the course followed by the excitation through the heart muscle. For a time it was thought that the ventricular portion of the electrocardiogram could be explained by assuming that it represents the algebraic sum of the curves resulting from the negativity of the base and the negativity of the apex. The difficulty, however, was to explain the *T*-wave, or in other words, why in such a resultant curve there should be two phases in the same direction. Bayliss and Starling thought they had found the solution in the assumption that the excitation of the base of the heart lasts longer than that at the apex. According to their view the ventricular portion of the curve begins with the negativity of the base. This produces the quick excursion *R*, to be followed by a rapid sinking due to the negativity of the apex. The wave *T* would then be due in their opinion to the fact that the base remains negative after the excitation process at the apex has ceased.

To explain the longer negativity of the base Gotch has put forward a view based upon the embryological development of the heart. As is well known, the heart is derived in the embryo from a simple tube which later becomes curved in the form of a loop. The apex of the ventricle corresponds more or less to the middle of this loop. The atria and part of the bases of both right and left ventricle belong to the beginning of the loop, while the region of the aortic bulb at the base corresponds to the end of the loop. If *a* be the base of the ventricle continuous with the atria and *b* the part of the base corresponding to the pulmonary artery and aorta and *c* to the apex of the heart, the excitation according to Gotch's view passes from *a* through *c* to *b*. In electrocardiography *a* and *b* are connected with one end of the galvanometer and *c* with the other. Thus, according to Gotch's ideas, the base of the heart remains negative for a longer time than the apex, not because the excitation process remains longer in one and the same spot, but because different parts of the base are excited at different times. If Gotch be right, then the wave *R* is due to the part of the base we have designated *a* and the wave *T* to the part of the base we have designated *b*. The stretch between *R* and *T* would then correspond to the period during which base and apex are simultaneously negative. As Gotch points out, the spread of the excitation in the heart must be more complex than that in a simple linear excitable structure, though the scheme of such a simple structure may help us to understand it.

Nicolai bases his explanation of the form of the electrocardiogram upon the newer ideas of the conduction path followed by the excitation process in the heart of man and higher animals. It is now generally believed that the atria are connected with the ventricles only by the atrio-ventricular bundle of His and its radiations, which, as Tawara has shown, become continuous with the Purkinje fibers and the papillary system; the papillary muscles in turn are connected with the external spiral fibers of the ventricle on the one hand and

with the circular muscle (*Treibwerk*) of the heart (Fig. 45). The excitation seems to pass from the atria to the papillary system and is conducted along this from the base of the ventricles to the apex and then extends from the apex into the spiral and circular fibers, finally returning to the base. Until the papillary system is reached the excitation follows a simple, undivided path and so might be expected to give rise to a diphasic current with opposite phases. According to Nicolai R and S are two such phases. The reason why S is followed by a horizontal stretch lies, in Nicolai's opinion, in the combined excitation of the spiral and circular fibers, since the action-currents thus set up reciprocally compensate for one another. When the excitation finally reaches the base again, so that the latter becomes strongly negative, the T-wave arises. Then all the activity of the heart muscle ceases during the pause until the next atrial excitation is indicated by the following P-wave.

According to Einthoven the P-wave is due to excitation of the atria. The horizontal stretch between P and Q is due to

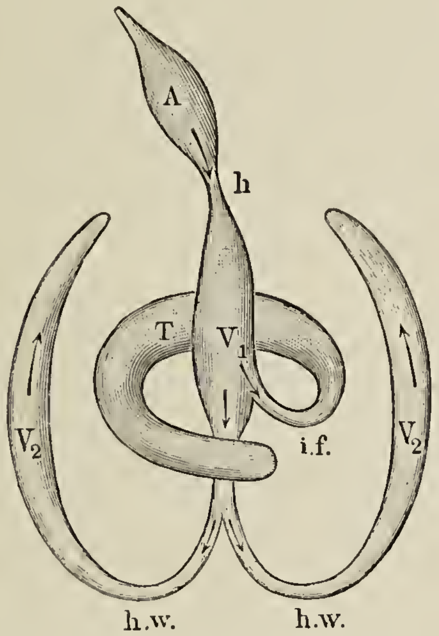


Fig. 45.—Scheme of the course of conduction in the cardiac muscle (after G. F. Nicolai). A, atrium; h, His bundle; V_1, papillary muscles; V_2, spiral fibers of ventricles; T, circular fibers or Treibwerck).

the passage of the excitation through the His bundle, during which the action-currents are so slight as not to register. Thence the excitation process is distributed to the walls of the ventricles, but in Einthoven's opinion a very large number of spots over the surface of the ventricle are simultaneously stimulated. The waves Q, R and S are the result. He thinks that if the stimulus happens to start close to the apex or in the left ventricle a Q-wave appears, while Q is absent if other spots in the ventricle are first excited. The excitation of the right ventricle, and especially of portions of the ventricular muscle at the base of the heart, gives rise to the R-wave, and the fact that this is immediately followed by an S-wave indicates, in his opinion, that almost immediately afterward the excitation of the left ventricle and of various spots near the apex of the heart got the upper hand. Then follows the horizontal stretch between S and T due, Einthoven thinks, to a rather even distribution of the excitation process over the whole ventricular walls. Should this general excitation stop at one time there is no T-wave, a phenomenon sometimes met with in degeneration or insufficiency of the heart. If the right ventricle stays contracted longer than the left, we get an upward T-wave in the first and second derivations, as is seen in all typical electrocardiograms. If the base of the heart stays contracted longer than the apex, we get an upward T-wave with D_3, while a downward wave with D_3 shows that the apex is longer contracted than the base. Einthoven states that in normal hearts the T-wave with D_3 may be either positive or negative, while with D_1 and D_2 it is always positive, higher after exertion and less marked when the heart is injured. A striking difference between Nicolai's explanation and Einthoven's is the difference of opinion regarding the waves R and S. While Nicolai assumes that this portion of the curve is a diphasic curve due to the spread of the excitation in a linear structure, Einthoven thinks that the appearance of this portion of the curve depends upon the inequality of excitation of various portions of the ventricle as a whole.

The similarity of the so-called atypical electrocardiogram (ventricular extrasystoles) to simple diphasic curves is very striking. Such curves are probably, Einthoven believes, due to the gradual advance of an excitation process from one end of a ventricle to the other. The stimulus here follows a course wholly different from that preceding normal contractions of the heart. It begins in the ventricles themselves, either close to the base or close to the apex, and may be propagated from the ventricles to the atria.

A somewhat different explanation of the form of the electrocardiogram from those offered above is to be found in the writings of Eppinger and Rothberger. Basing their views upon their experiments in which they injected sublimate and silver nitrate into the walls of the right and left ventricles they come to the following conclusions: The ascent of the R-wave is synchronous with the beginning of the excitation in the actual wall of the ventricle, whereas the pause between P and R includes, they believe, the whole period of excitation and conduction from the wall of the atrium to the termination of Tawara's conduction-system. This process of stimulus-conduction is not evident in any way in the electrocardiogram. Only on the arrival of this stimulus to a whole series of points upon the inner walls of the ventricles at the termini of the conduction-system does the ventricular part of the electrocardiogram begin. From this moment on (or even a little earlier if a Q-wave is present) up to the end of the T-wave the electrocardiographic curve represents, they say, the resultant of two antagonistic forces, the one sending a wave up lasting longer than that tending to send a wave down. It is probable, they think, that each of these forces is in turn the resultant of a large number of electrical forces corresponding to the multiple sites of stimulation. It is believed further by Eppinger and Rothberger that these two practically antagonistic forces correspond to the two main subdivisions of the cardiac muscle, the longitudinal (or spiral) fibers and the circular fibers. The circular fibers lie chiefly in the wall of the left ventricle; the longitudinal fibers are present in both

right and left ventricles. In the left ventricle the tissue at the apex and the papillary system are composed of longitudinal fibers. In the right ventricle nearly all of the wall is composed of these fibers, though one must bear in mind that the direction of the longitudinal muscle fibers is somewhat different in the part of the right ventricle into which the right atrium pours its blood from that of the longitudinal fibers in the portion of the same ventricle corresponding to the pulmonary infundibulum.

The longitudinal fibers are antagonists of the circular fibers; whereas the latter narrow and lengthen the heart, the former shorten and widen it. The two sets of fibers acting together bring about the greatest possible diminution of intraventricular space. Eppinger and Rothberger believe that these antagonistic muscles may be responsible for opposite effects in the electrocardiogram. It is the circular fibers, they think, which cause descent of the curve and the longitudinal fibers which bring about ascent thereof. If you destroy one set of these fibers with silver nitrate the other set will predominate. These ideas correspond to the electrocardiographic curves recorded in their experiments and they believe that the antagonism of the two ventricles in the electrocardiogram is dependent more upon the difference in anatomical structure than upon relations to base and apex.

All are agreed that clinical cases presenting hypertrophy of the right ventricle yield a large *R*-wave while hypertrophy of the left ventricle expresses itself in the form of a large *S*-wave. In the former instance the longitudinal system of fibers would be increased, while in the latter the circular.

These authors fall back upon the same hypothesis to explain the forms of the atypical curves associated with ventricular extrasystoles. If the extrasystole starts in the right ventricle and extends from it to the left there will be first a large *R*-wave on account of the predominant direction of longitudinal fibers, followed later by a large *S*-wave due to the extension of the excitation to the circular fibers of the left ventricle; similarly, when the extrasystole arises in the left ventricle the first large wave of the atypical electrocardiogram will be in the downward direction, to be followed later by a second large wave in the upward direction.

Since the longitudinal fibers of both ventricles contract before the circular fibers of the left ventricle the reason for the early appearance of the *R*-wave is, they think, explained.

The sudden fall of the *R*-wave is due, they think, to the sudden arrival of the excitation in the circular fibers. If the latter be destroyed, as in their silver nitrate experiments, there is no descent of the *R*-wave until much later.

Eppinger and Rothberger in their descriptions sometimes fall into an error of which they accuse other authors; namely, the confounding of the phenomenon of contraction with that of excitation. If one bear this fact in mind, however, it is easy to understand their meaning and certainly the results of their experiments are most suggestive.

No satisfactory explanation of the *T*-wave has, as yet, been given. Eppinger and Rothberger are much impressed by the fact that freezing of the surface of the ventricle affects only the *T*-wave and they believe, therefore, that the presence of this wave can have nothing to do with the excitation of the deeper muscular layers.

From the whole discussion it is obvious that much more work must be done before we shall attain to unanimity of opinion regarding the interpretation of the form of the typical electrocardiogram.

Phonocardiograms.

Another advance in cardiac investigation of recent date should be referred to briefly, namely, phonocardiogram-work.

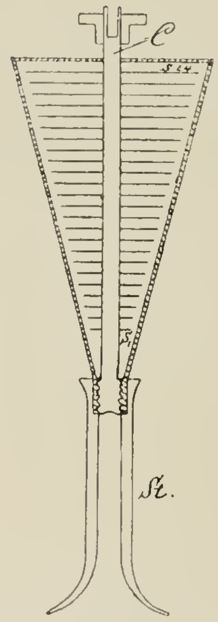


Fig. 46.

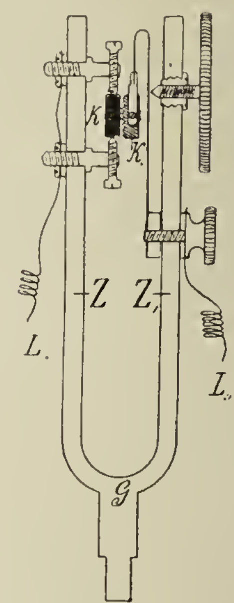


Fig. 47.

Fig. 46.—Resonance apparatus for strengthening the heart sounds. *St.*, stethoscope (after Hürthle).

Fig. 47.—Microphone for the registration of the heart sounds (after Hürthle).

The present status of the subject is described in the pamphlet of Otto Weiss [c] which should be consulted for details; here I shall call attention to the more interesting points only.

A knowledge of the exact relations of the contractions of the heart muscle and the moments when the heart sounds begin is of great importance for the accurate diagnosis of

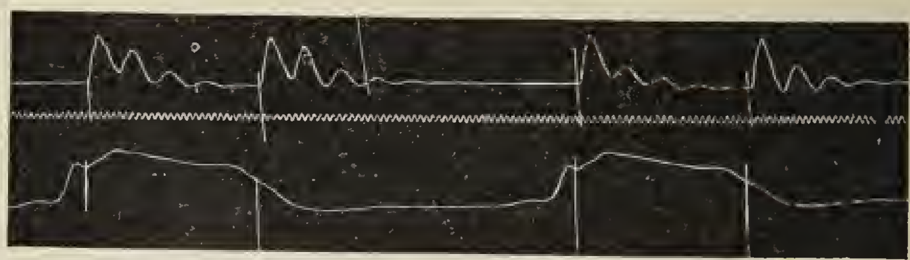


Fig. 48.—Registration of the heart sounds by Hürthle's method. In the upper curve the heart sounds are registered; the middle curve shows the time in one-hundredths of a second; the lower curve is the cardiogram.

cardiovascular conditions and efforts have, therefore, for a long time been made to register the heart sounds by mechanical means. The small energy of the sounds has made this very difficult, especially as it has been desired to have methods independent of the subjective reactions of the listening observer, methods which will have all the precision and objectivity of purely physical procedures.

[c] Weiss (Otto), Phonokardiogramme, Jena, 1909.

The subjective "marking method" which has been most used is that of Martius; it was of value especially in the analysis of clinical cardiograms but its faults have been pointed out especially by Hürthle.

FIG. 49.—Temporal relations between the heart sounds and the cardiogram in man (after Einthoven). *C*, cardiogram; *I*, first heart sound; *II*, second heart sound.

In working out objective methods for registering the heart sounds it was necessary to transfer the sound-vibrations to then act upon the handle *G* of a wooden tuning fork, with the arms *Z* and Z_1, the latter being set into vibration in the same tempo; the vibrations of the arms of the fork excite

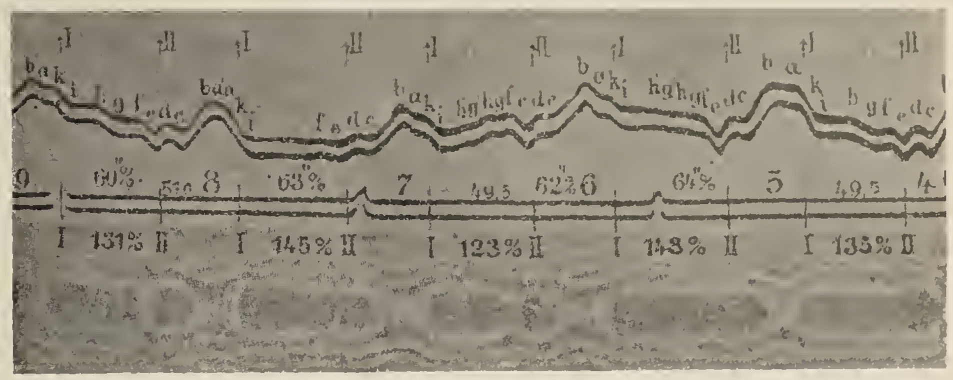


FIG. 53.—Registration of human heart sounds by Holowinski's method. Only a part of the author's figure is reproduced.

the microphone (Fig. 47); this sets in action an electromagnetic signal-apparatus and the movements are transferred to a pantograph of Marey and registered (Fig. 48).

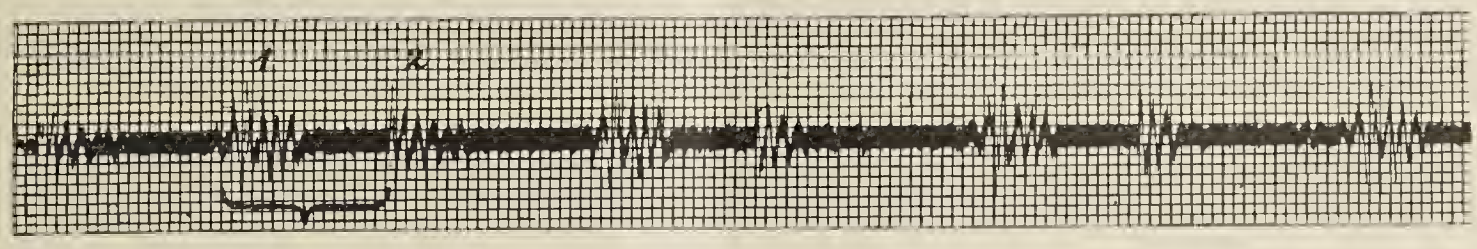


FIG. 50.—Registration of the apical heart sounds (after Einthoven). *I*, first heart sound; *II*, second sound.

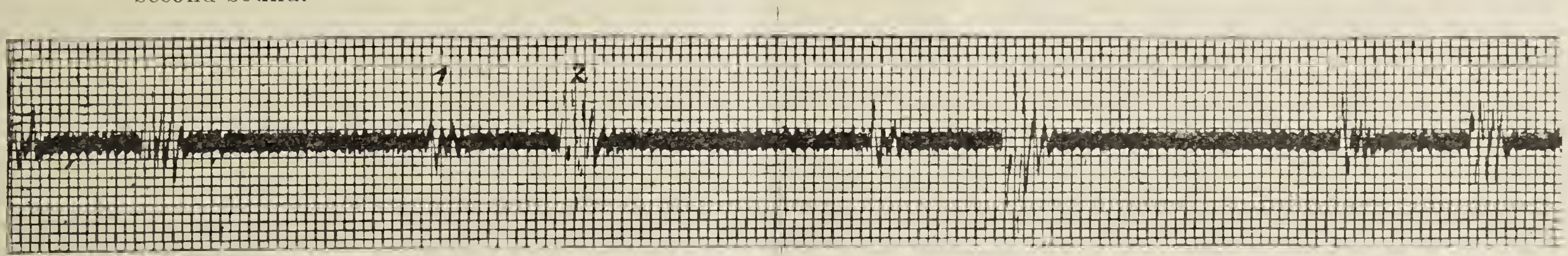


FIG. 51.—Registration of the sounds over the pulmonic area in man (after Einthoven). *I*, first sound; *II*, second sound.

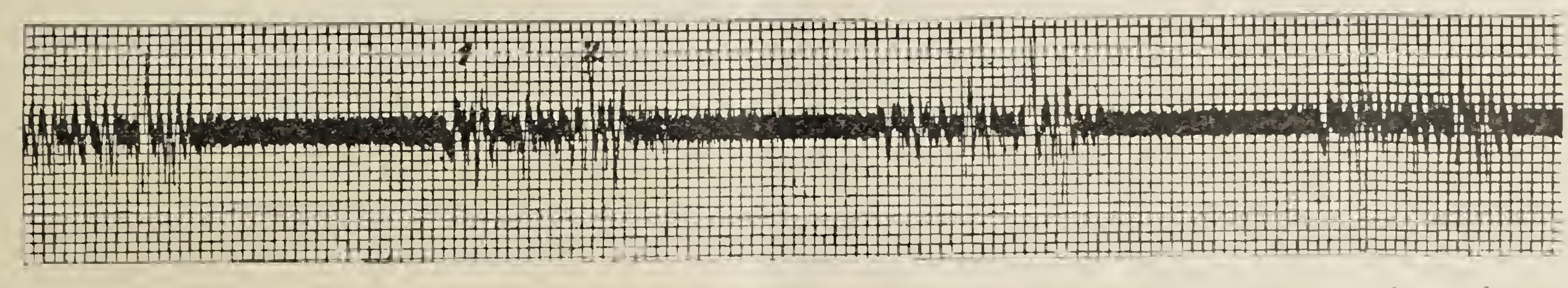


FIG. 52.—Registration of systolic heart murmur (after Einthoven). *I*, first sound; *II*, second sound.

some apparatus which would be set into sympathetic vibration (by resonance) and then to register these. The difficulties in the way were twofold: (1) the existence of vibrations of the chest wall other than those due to the heart sounds, and (2) the small amount of energy represented by the heart sounds themselves. Both difficulties have been overcome, the latter by devising receiving and recording apparatus of extreme delicacy. Three different investigators—Hürthle, Einthoven and Holowinski—have employed methods in which the sounds are received by means of a microphone.

Hürthle receives the heart sounds by a stethoscope (*St*) connected with a resonance-apparatus, which magnifies the amplitude of the vibrations (Fig. 46); the enlarged vibrations

Einthoven also receives the sounds by a microphone. At first he used for registration the capillary electrometer, but later employed the more delicate string galvanometer. His findings of the relation of the heart sounds are shown in Fig. 49. In Figs. 50 and 51 the differences in intensity and duration of the heart sounds at the apex and at the base of the heart are well illustrated. In Fig. 52 is reproduced Einthoven's findings in a case of mitral, insufficiency with systolic murmur. In Fig. 2 of my Jerome Cochran lecture (this Bulletin, 1909, p. 299) I have introduced one of Einthoven's phonocardiograms showing the position of the normal "third sound" of the heart. One great difficulty in working with the microphone lies in the necessity of making the ob-

servations in an absolutely quiet place; the vibrations of an elevator or of people walking about in the neighborhood disturb the records.

Holowinski also uses a microphone as a receiver of the heart sounds, but records them with the aid of a so-called "optical telephone." The method depends upon an application of the interference-rings of Newton; the changes in the rings are photographed, as shown in Fig. 53. For the details of the method Holowinski's article should be consulted.

Fig. 54.—Registration of human heart sounds by Marbe's method. *I*, first sound; *II*, second sound.

Marbe has used an entirely different objective method for recording the heart sounds. Recalling König's studies on the transfer of oscillations of a tambour to a gas flame of great sensibility he applied his instrument to the chest over the heart, and lighting the acetylene gas, passed a paper through the sooty flame; he got very good records of the heart sounds in the form of sooty rings as shown in the tracing (Fig. 54). A record has been made by Roos with this method from a patient with stenosis and insufficiency of the mitral valve.

A third principle—that of registering *directly* the oscillations of the sound-receiving membrane—has been utilized by O. Frank, by Gerhartz and by O. Weiss. The most important result of the application of the principle seems to be the invention of the *phonoscope* by Weiss. This investigator receives the sounds on a soap bubble, a membrane which exceeds in delicacy even the most sensitive microphone as yet devised. The difficulty of registering the oscillations of such a fragile and sensitive structure is obvious, but Weiss overcame it in the following way: He placed one end of a silvered glass thread bent at a right angle (0.01 mm. in diameter, weighing 0.0000035 gm.) in the center of the soap bubble, the other end being fastened in a holder; the oscillating bubble transfers its vibrations to the glass lever and the movements of the latter are registered photographically. Weiss gives an exact description of this phonoscope in his monograph; the apparatus is pictured in Figs. 55 and 56. In order that the vibrations of the heart sounds only shall effect the soap bubble, Weiss excludes the slow air-movements due to the chest wall (heart impulse) by placing the patient in a large iron guard containing a receiving-funnel which is pressed against his chest; the tube from this funnel projects in the phonoscope tube, but a space of about 4 mm. play is left between the two tubes. By such an unclosed connection of the sound-conducting apparatus with the phonoscope, the disturbing effects of the chest-wall vibrations are prevented.

The relations between the heart sounds and the different phases of the cardiogram tracing seem to be inconstant, a finding by Weiss, which is in accord with general clinical experience regarding the uncertainties of cardiograms. On the

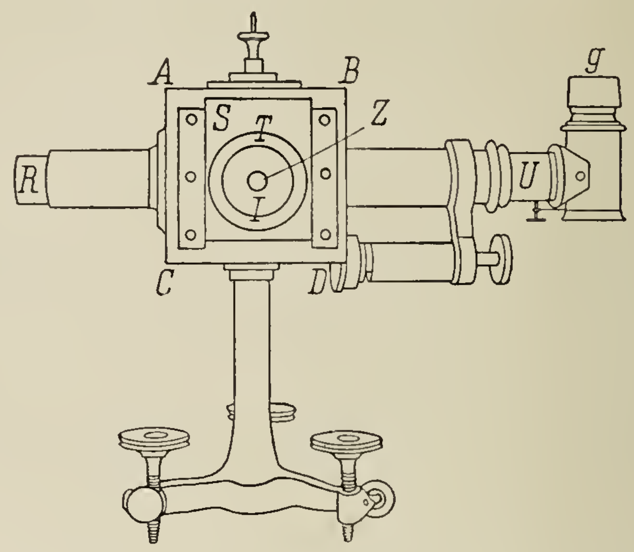


Fig. 55.—The phonoscope (after O. Weiss, Phonokardiogramme, Jena, 1909, 23, Fig. 20).

other hand, the temporal relations between the carotid pulse and the heart sounds are peculiarly constant in health; the time elapsing between the beginning of the first heart sound and the ascent of the carotid pulse amounts to 6.75 or 7.75

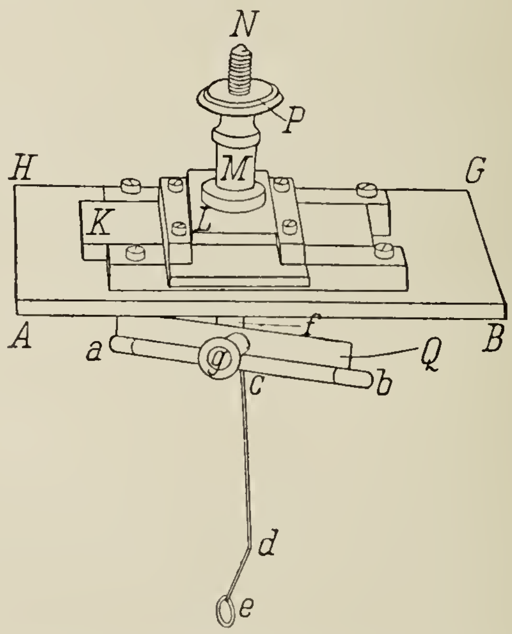


Fig. 56.—View of the upper part of the phonoscope (after O. Weiss, Phonokardiogramme, Jena, 1909, 23, Fig. 21).

hundredths of a second (Fig. 57). Weiss has been able with his method to record the fœtal heart sounds in a pregnant woman; in the case he examined the rate was 147 beats per

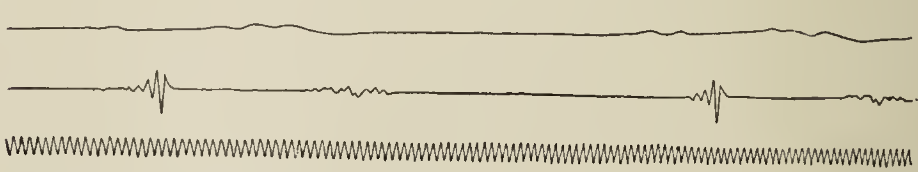


Fig. 57.—Registration of heart sounds in man by Weiss's method. The curve of the carotid pulse is shown above, the phonocardiogram in the middle and the time markings of 0.01 sec. below (after O. Weiss, Phonokardiogramme, Jena, 1909, 25, Fig. 24). Curves are to be read from right to left.

minute, the systole lasting 18.2 and the diastole 22.6 hundredths of a second.

Important as these results of Weiss are for physiology, to

us clinicians the findings of Joachim with the same method in pathological hearts are even more interesting. Joachim's studies include observations in the sounds and their temporal relations to the carotid pulse in cases of (1) mitral insufficiency; (2) mitral stenosis; (3) aortic insufficiency; (4)

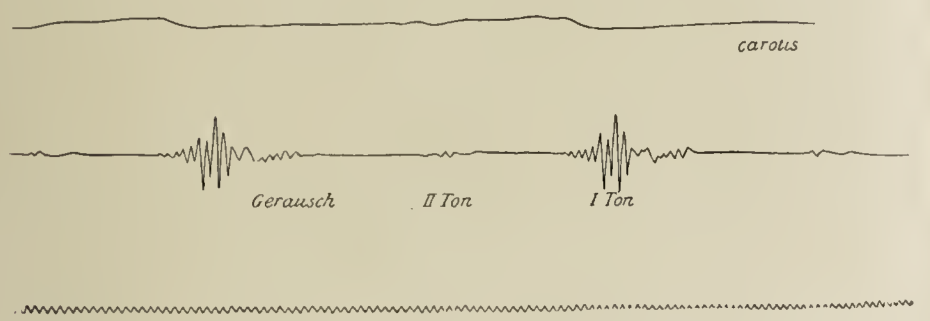


FIG. 58.—Phonocardiogram in mitral stenosis. Carotid pulse tracing above; time markings of 0.01 sec. below (after O. Weiss, Phonokardiogramme, Jena, 1909, 29, Fig. 30).

combined stenosis and insufficiency at the aortic orifice, and (5) functional (anæmic) murmurs. Doublings and splittings of the heart tones have also been studied in this way.

In Figs. 58 and 59 I have introduced two curves illustrating mitral stenosis; they are very characteristic—one could make the diagnosis from the curves alone. In Fig. 58 the murmur is presystolic, while in Fig. 59 it lasts through the whole of diastole (note that these tracings are to be read from right to left).

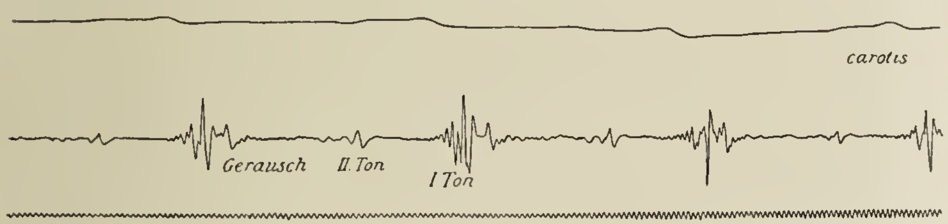


FIG. 59.—Phonocardiogram in another case of mitral stenosis (after O. Weiss).

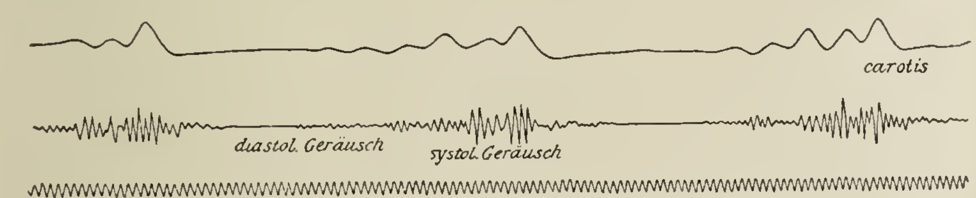


FIG. 60.—Phonocardiogram in aortic stenosis with aortic insufficiency. Arteriogram above (after O. Weiss).

A patient with aortic stenosis and insufficiency yielded the curves shown in Fig. 60. It is seen that the systolic murmur here is maximal at the time the carotid pulse is maximal. In mitral insufficiency the systolic murmur is maximal before the pulse appears in the carotid. These results confirm, therefore, von Noorden's view of the temporal discrepancy of these two kinds of systolic murmur.

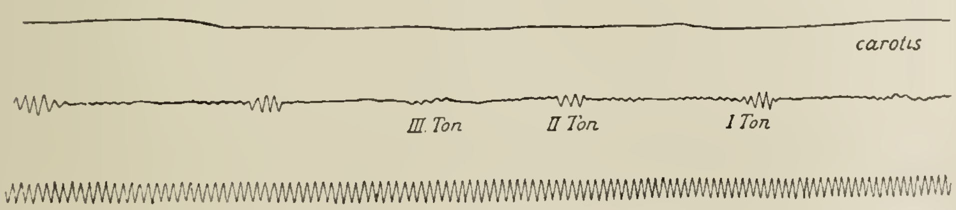


FIG. 61.—Phonocardiogram of three-time rhythm (protodiastolic gallop) (after O. Weiss).

The sounds in a protodiastolic gallop-rhythm are recorded in Fig. 61. Observe that the third tone lies closer to the preceding second sound than it does to the following first sound. The times as actually measured are 0.17 and 0.21 seconds respectively.

As Weiss suggests, we may expect to learn something later on by simultaneous recording of electrocardiograms and phonocardiograms.

THE TELEPHONE STETHOSCOPE.

Very recently a highly ingenious device in the form of a telephonic stethoscope has been invented by S. G. Brown. It depends upon the application of a telephone relay, which in turn is based upon the modern researches of physicists concerning the flow of electrons across a microscopic air-gap between two conducting surfaces at different potentials. Telephonic currents passing through the relay have their strength increased almost twenty-fold, and apparently still greater intensifications may be obtained by placing two relays in tandem, by which the intensification becomes four-hundred-fold.

In the electrical stethoscope, a diagrammatic view of which is reproduced in Fig. 62, the sound of the heart beat is, with

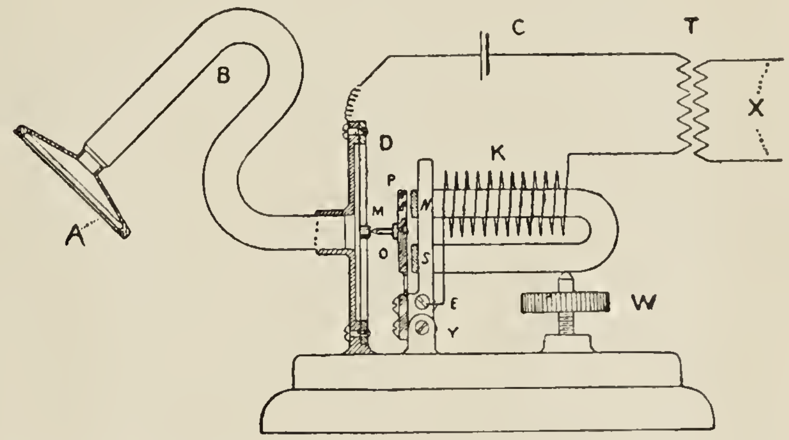


FIG. 62.—Diagrammatic view of Browne's telephonic stethoscope (by courtesy of Scientific American, 1910, CII, Fig. 4).

the aid of a transformer, intensified about 60 times. The study of pathological cases with this instrument has been begun in the London Hospital, where, it is said, the physicians are much pleased with its promise.

"Long-distance" auscultation of the heart and lungs is now feasible. Brown's instrument can be attached to the long-distance telephone service; by means of it the heart sounds of a person in London have already been listened to, and heard distinctly, by physicians in the Isle of Wight—a distance of about 100 miles.

I see no reason why this instrument should not be combined with a graphophone and permanent records be made of heart sounds; they might then be reproduced at will before medical societies or classes in physical diagnosis. Weiss has reproduced mechanically recorded heart-sounds with the help of a telenium-cell, battery and telephone.

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NOTES AND NEWS.

ADDITIONAL HUMAN EMBRYOS.

Professor Mall, of the Johns Hopkins University, again requests that physicians send him embryological specimens which are constantly falling into their hands. The collection of such specimens at the Johns Hopkins Medical School is now one of the best in existence, has been studied carefully by the staff here, and is being used constantly by anatomists at home and abroad. About 100 published studies on human embryology are based upon this collection, including the "Manual of Human Embryology" in two volumes, published recently by the J. B. Lippincott Co.

Much more material than is now at hand is needed by investigators to further the science of human embryology as well as to study with greater care the diseases of the ovum and the cause of abortion. To make material of greatest value it should be preserved immediately after the abortion in a 10 per cent solution of formalin, or by more refined methods, if they are at hand. Small specimens should not be dissected, but should be preserved entire in formalin. Of very great value are good histories of the cases, for through them we may discover the cause of abortions, and ultimately their cure. Studies of this kind enable embryologists to be of use to physicians in active practice. Specimens should be packed in bottles filled *completely* with the preserving fluid, and not wrapped in cotton. If there are no air spaces in the bottle, no amount of shaking will injure the most delicate embryo. Small specimens may be sent by mail, while larger ones should be sent by express, collect charges, to

DR. F. P. MALL,
Johns Hopkins Medical School, Baltimore, Md.

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ILLUSTRATIONS.

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